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(57) Abstract

RGD mimetics which combine a nitroaryl moiety with an arylether/α–aminoacid/guanidine framework exhibit activity as antagonists toward various integrins and as inhibitors of angiogenesis.

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# ANGIOGENESIS INHIBITORS

## SPECIFICATION

Technical Field:

The present invention relates to nonpeptide compounds having RGD mimetic activity and to the synthesis and biological activity of nonpeptide compounds having RGD mimetic activity. More particularly, the present invention relates to nitroaryl based nonpeptide RGD mimetics and to their synthesis and biological activity.

Background:

The integrins are a class of extracellular proteins that facilitate cell-cell and cell-matrix adhesion (Cheresh, D.A.; Mecham, R.P. Eds.; Academic Press: New York, 1994; Stromblad, S.; Cheresh, D.A. Chem. Biol. 1996, 3, 881) These important biological targets are membrane bound, heterodimeric glycoproteins made up of an α-subunit and a smaller β-subunit. The relative affinity and specificity for ligand binding is determined by the unique combination of the different α- and β- subunits. Of the members of this family of receptors, $\alpha_{IIb}\beta_3$, $\alpha_5\beta_1$, $\alpha_v\beta_3$, and $\alpha_v\beta_5$ are the most studied. A number of known natural ligands to these integrins, such as fibronectin (binds to $\alpha_5\beta_1$), fibrinogen (binds to $\alpha_{IIb}\beta_3$) and vitronectin (binds to $\alpha_v\beta_3$), contain the key peptide sequence Arg-Gly-Asp (RGD) within their native sequence, which is recognized by most integrins. The $\alpha_{IIb}\beta_3$ integrin was shown to be an excellent target for the inhibition of platelet aggregation and several groups have already disclosed the design and synthesis of potent binders with peptide and nonpeptidal structures (Ojima et al. Bioorg. Med. Chem., 1995, 337; Engleman et al. Ann. Rep. Med. Chem. 1996, 31, 191).

Within the context of angiogenesis, the functions of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ have been shown to be vital. Cheresh and coworkers have shown that in vivo inhibition of binding of these

integrins to their RGD-containing ligands by antibodies or cyclic peptides interferes with angiogenesis and induces tumor regression (Brooks et al. Science 1994 et al. Rosenfeld et al. Cell 1994, 79, 1157). In addition to its relevance to angiogenesis, $\alpha_v\beta_3$ has also been known to play a role in mediating adhesion of osteoclasts to the bone matrix and in the migration of vascular smooth muscle cells.

Antagonists of $\alpha_v\beta_3$ are, therefore, envisioned as potential therapeutic agents for the treatment of numerous disease states such as diabetic retinopathy, cancer, osteoporosis and restenosis (Van der Pluijm et al. Bone Mineral Res. 1994, 9, 1021; Helfrich et al. J. Bone Mineral Res. 1992, 7, 335; Horton et al. Exp. Cell Res. 1991, 195, 368; Robey et al. Ann. Rep. Med. Chem. 1993, 28, 227; Choi et al. Surgery 1994, 19, 125; Matsuno et al. Circulation 1994, 90, 2203; Hammes et al. Nature Med. 1996, 2, 529; Friedlander et al. Proc. Natl. Acad. Sci., USA 1996, 93, 9764.

The first small molecule antagonists of $\alpha_v\beta_3$ were reported by Kessler et al. (e.g. 1, Figure 1; Gurrath et al. Eur. J. Biochem. 1992, 210, 911; Muller et al. Angew. Chem. Int. Ed. Engl. 1992, 31, 326; Aumailley et al. FEBS Lett. 1991, 291, 50; Pfaff et al. J. Biol. Chem. 1994, 269, 20233; Haubner et al. J. Am. Chem. Soc. 1996, 118, 7461). Subsequently, groups from Dupont-Merck (e.g. 2, Figure 1) and SmithKline Beecham (SKB) (e.g. 3, Figure 1) published their results in the field. In addition, other RGD containing cyclic peptides 4 and 5 (Figure 1) were synthesized and shown to be active by Burgess et al. and Goodman et al. respectively (Bach et al. J. Am. Chem. Soc. 1996, 118, 293; Peishoff et al. J. Med. Chem. 1992, 35, 3962; Burgess et al. J. Med. Chem. 1996, 39, 4520; Tran et al. Bioorg. Med. Chem. Lett. 1997, 7, 997).

More recently a number of groups reported their results with high affinity ligands for $\alpha_v\beta_3$ possessing structures

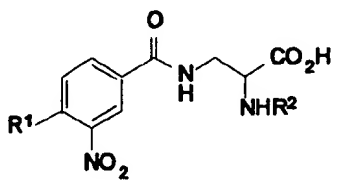
significantly deviating from classical peptide frameworks (e.g. 6-9, Figure 2). These structures contain a central scaffold (e.g. benzene, benzodiazepine-type or urea backbone) onto which appendages carrying carboxylate and guanidino groups are attached (Duggan et al. Abstracts of Papers, 211th ACS National Meeting, New Orleans, LA, March 24-28, 1996; American Chemical Society: Washington, DC, 1996, MEDI 234; Keenan et al. J. Med. Chem. 1997, 40, 2289; Corbett et al. Bioorg. Med. Chem. Lett. 1997, 7, 1371; Gadek et al. Abstracts of Papers, 211th ACS National Meeting, New Orleans, LA, March 24-28, 1996; American Chemical Society: Washington, DC, 1996, MEDI 235; Hirschmann et al. J. Am. Chem. Soc. 1996, 115, 12550).

What is needed are synthetically accessable RGD mimetics which posses stability *in vivo* with high activity and selectivity against various integrin targets. Furthermore, what is needed is an efficient and general method to produce such compounds.

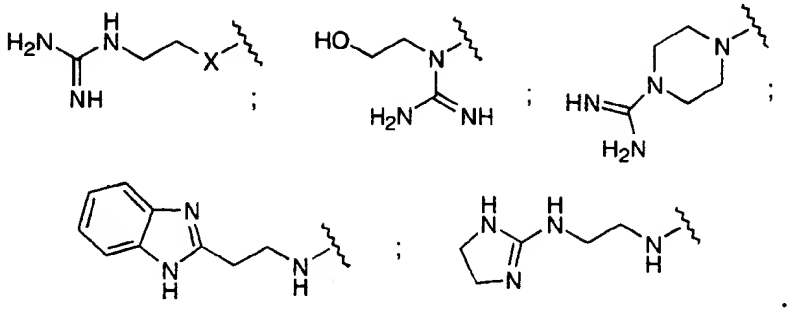
Summary of the Invention:

The invention is directed to the design, chemical synthesis and biological evaluation of a series of nitroaryl-based RGD mimetics. More particularly, the invention is directed to compounds which combine a novel nitroaryl system with arylether/α-aminoacid/guanidine frameworks of the type disclosed in U.S. Patent No. 5,741,796, issued April 21, 1998, incorporated herein by reference, i.e., the "Merck compounds".

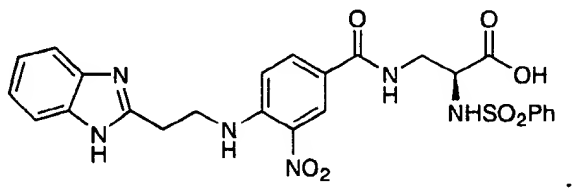
One aspect of the invention is directed to an RGD mimetic represented by the following structure:



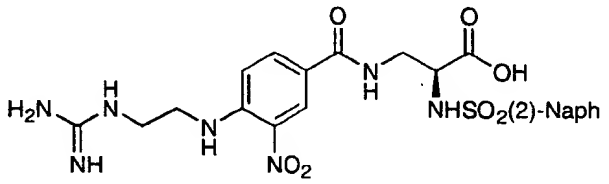
In the above structure, $R^1$ is selected from the following radical:



Here, **X** is a diradical selected from sulfur, -NH- and oxygen. $R^2$ is a radical selected from $-CO_2t$-Butyl, -CO-Aryl and $-SO_2$-Aryl. Preferred **Aryls** include phenyl, 1-naphthyl, and 2-naphthyl. A preferred $R^2$ radical is $-SO_2$-Aryl. A preferred RGD mimetic is represented by the following structure:



Other preferred RGD mimetics are represented by the following structures:



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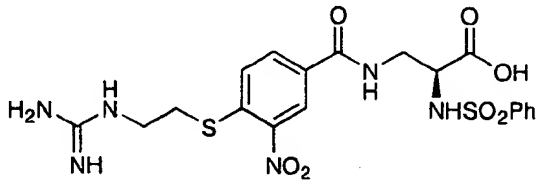

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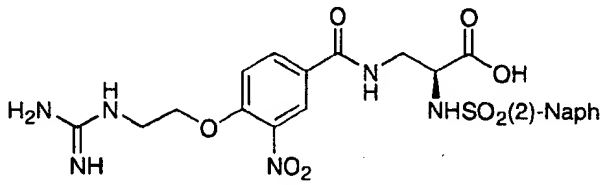

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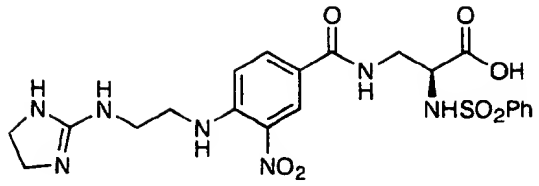
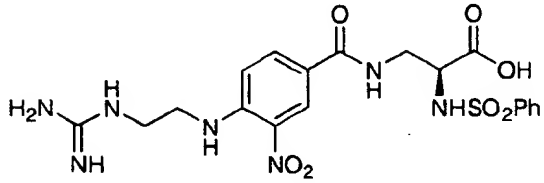
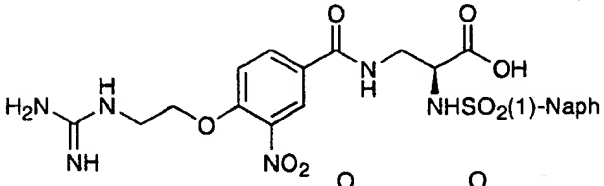

O
O
N
H
OH
NHSO2Ph
H
N
H
N
N
H
N
NO2

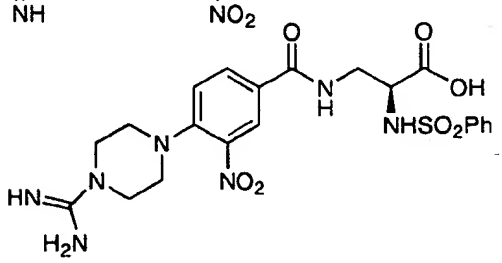
;


O
O
N
H
OH
NHSO2Ph
H2N
H
N
NH
N
H
NO2

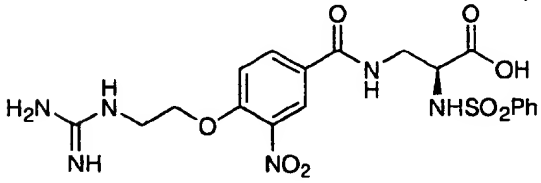
;


O
O
N
H
OH
NHSO2(1)-Naph
H2N
H
N
NH
O
NO2

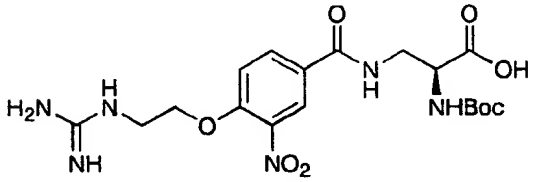
;


O
O
N
H
OH
NHSO2Ph
N
N
NO2
HN
H2N

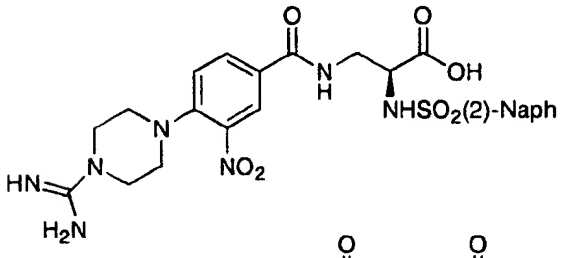
;


O
O
N
H
OH
NHSO2Ph
H2N
H
N
NH
O
NO2

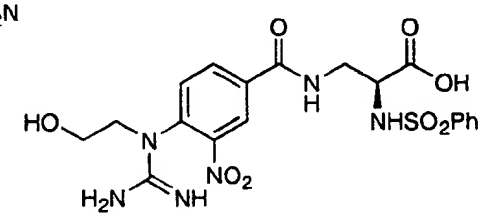
;


O
O
N
H
OH
NHBoc
H2N
H
N
NH
O
NO2

;

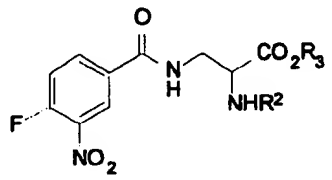

O
O
N
H
OH
NHSO2(2)-Naph
N
N
NO2
HN
H2N

; and


O
O
N
H
OH
NHSO2Ph
HO
N
NO2
H2N
NH

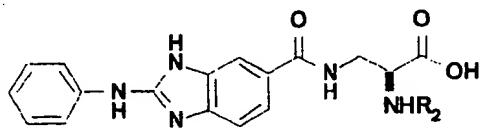
.

Another aspect of the invention is directed to a method for producing the above RGD mimetics. Firstly, a nitroaryl precursor is provided having a fluoride group covalently attached to the nitroaryl ring represented by the following structure:



In the above structure, $R_3$ is an acid protecting group. Then, the fluoride group is displaced with a nucleophile having a protected guanidine group using nucleophilic aromatic substitution for producing a protected RGD mimetic. Finally, the protected RGD mimetic is deprotected with an acid for producing the RDG mimetic.

Another aspect of the invention is directed to an RGD mimetic represented by the following structure:

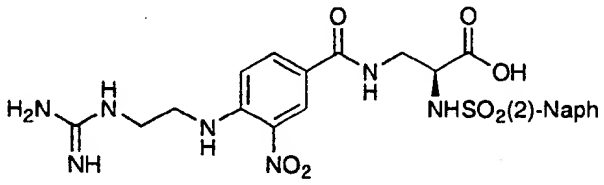


In the above structure, $R^2$ is a radical selected from a group consisting of -$CO_2$*t*-Butyl, and -$SO_2$-Aryl. Preferred **Aryls** include phenyl, 1-naphthyl, and 2-naphthyl.

The above RGD mimetics were tested against a variety of integrins ($\alpha_v\beta_3$, $\alpha_{IIb}\beta_3$ and $\alpha_v\beta_5$) for their ability to inhibit cell adhesion and in order to determine their binding selectivity. Selected compounds were also tested for their ability to inhibit angiogenesis in vivo in the CAM (chick chorioallantoic membrane) assay. All compounds were verified to have inhibitory activity and selectivity against the above targets, consistant with their activity as inhibitors of

angiogenesis.

Another aspect of the invention is directed to a process for differentially inhibiting $\alpha_{iib}\beta_3$ mediated cell adhesion over $\alpha_v\beta_3$ mediated cell adhesion. Cells that express $\alpha_{iib}\beta_3$ are contacted with a solution containing selected RGD mimetics. The solution has a concentration of such RGD mimetics sufficient for inhibiting $\alpha_{iib}\beta_3$ mediated cell adhesion. As a result, $\alpha_{iib}\beta_3$ mediated cell adhesion is inhibited at least approximately 100 fold more than $\alpha_v\beta_3$ mediated cell adhesion. Preferred RGD mimetics employable for this aspect of the invention are as follows:

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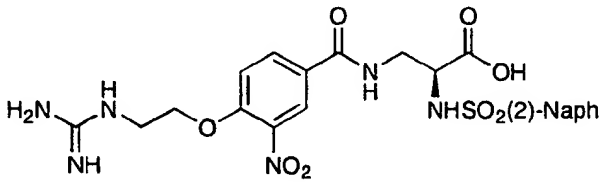


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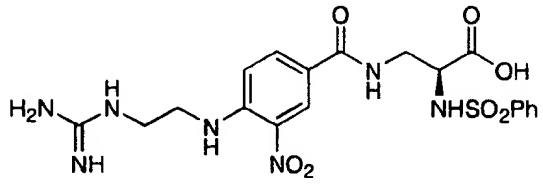


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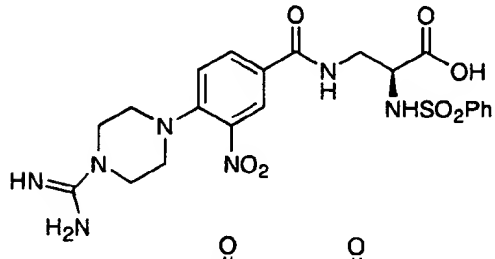


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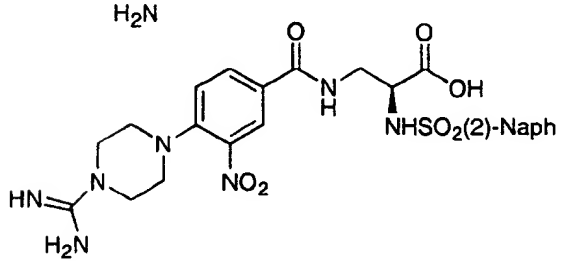


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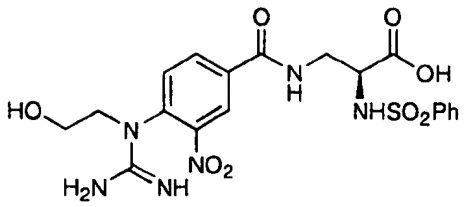


Description of Figures:

Figure 1 illustrates selected structures of $\alpha_v\beta_3$ antagonists based on the RGD peptide sequence.

Figure 2 illustrates selected nonpeptide RGD mimetics with high affinity for $\alpha_v\beta_3$.

Figure 3 illustrates targeted nitroaryl ethers (10-21) as RGD mimetics and benzimidazole 22.

Figure 4 illustrates general structures of nitroarylether RGD mimetics and retrosynthetic analysis.

Figure 5 illustrates synthesis of amino esters 26, 29a and 29b with the following *Reagents and conditions:* (a) 1.1 equivalents of $Boc_2O$, 1.0 equivalent of $Na_2CO_3$, 1,4-dioxane, $H_2O$, 25°C, 88%; (b) *i)* 20% aqueous solution of $Cs_2CO_3$, H2O:MeOH (1:2.5), 25°C, 4 hours, 100%, *ii)* 1.1 equivalents of BnBr, DMF, 25°C, 14 hours, 88%; (c) 1.5 equivalents of $PhI(OCOCF_3)_2$, DMF:$H_2O$ (1:1), 2.0 equivalents of pyridine, 25°C, 3.5 hours, 41%; (d) 1.1 equivalents of $ArSO_2Cl$, 2.25 equivalents of NaOH, dioxane:$H_2O$ (1:2), 0 to 25°C, 3 hours, [71% for 27a, 66% for 27b]; (e) 1.3 equivalents of $Br_2$, 9.2 equivalents of NaOH, $H_2O$, 0 to 90°C, [75% for 28a, 81% for 28b]; (f) isobutylene, 2.8 equivalents of conc. $H_2SO_4$, DME, -78 to 25°C, 48 hours, [55% for 29a, 51% for 29b]. DME = dimethoxyethane; DMF = dimethylformamide; Ph = phenyl; 2-naphthyl.

Figure 6 illustrates the synthesis of compounds 10 - 13.

with the following *Reagents and conditions*: (a) 5.0 equivalents of $MeC(OMe)_3$, PhMe, 80°C, 8 hours, 98%; (b) 1.1 equivalents of $N_3(CH_2)_2OTBS$, 0.1 equivalents of TBAF, 4 Å MS, DMF, 25°C, 4 hours, 73%; (c) 2.0 equivalents of $LiOH \bullet H_2O$, 3:1 dioxane:H2O (3:1), 25°C, 4 hours, 99%; (d) 1.0 equivalent of DCC, 0.2 equivalents of 4-DMAP, $CH_2Cl_2$, 25°C, 4 hours, 82%; (e) 50% TFA in $CH_2Cl_2$, 25°C, 2 hours, 84%; (f) 1.1 equivalents of $PhSO_2Cl$ or 1-$NaphSO_2Cl$, 1.3 equivalents of *i*-Pr2NEt, $CH_2Cl_2$, 25°C,4 hours, 38a (78%), or 38b (57%); (g) 2.0 equivalents of $Ph_3P$, 44 equivalents of $H_2O$, THF, 25°C, 12 hours, 80%, *ca.* 1:1 of 35a:35b; 80%, *ca.* 1:1 of 39a:41a; 81%, *ca.* 1:1 of 39b:41b; (h) 2.0 equivalents of $LiOH \bullet H_2O$, $THF:H_2O$ (3:1), 25°C, 4 hours, 93-99% for 36ab, 40ab, 42a; (i) 1.1 equivalents of 1*H*-pyrazole-1-carboxamidine•HCl, 1.1 equivalents of *i*-$Pr_2NEt$, DMF, 25°C, 16 hours, 13-15% for 10, 11, 13; 50°C, 16 hours, 5% for 12, after RP-HPLC. TFA = trifluoroacetic acid; TBAF = tetra-*n*-butylammonium fluoride; DCC = 1,3-dicyclohexylcarbodiimide.

Figure 7 illustrates the snthesis of guanidine derivatives 51 - 56 with the following *Reagents and conditions*: (a) 1.0 equivalent of B*t*BMTP, 2.0 equivalents of $Et_3N$, 1.0 equivalent of $HgCl_2$, DMF, 25°C, 4 hours, 98%; (b) 1.0 equivalent of B*t*BMTP, DMF, 25°C, 14 hours, 95%; (c) 1.0 equivalent of B*t*BCT, DMF, 25°C, 14 hours, 60%; (d) 0.2 equivalents of B*t*BMTP, 0.4 equivalents of $Et_3N$, 0.2 equivalents of $HgCl_2$, DMF, 25°C, 4 hours, 51%; (e) 0.66 equivalents of *o*-$NH_2C_6H_4NH_2$, 5.5 N aqueous HCl, reflux, 24 hours, 73%; (f) 1.0 equivalent of DmPD•HBr, *i*$Pr_2NEt$, DMF, 25°C, 11 hours, 51%. Boc = *tert*-butoxycarbonyl; B*t*BCT = *N, N'* - Bis-*tert*-butoxycarbonylthiourea; B*t*BMTP = 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2- thiopseudourea; DmPD•HBr = 2-(3,5-dimethylpyrazolyl) -4,5-dehydroimidazole hydrobromide.

Figure 8 illustrates the synthesis of compounds 11 and 14-19 with the following reagents and conditions: (a) 1.2 equivalents of $(COCl)_2$, PhH, DMF, 0°C, 6 hours, 99%; (b) 1.0 equivalent of 29a or 29b, 1.2 equivalents of $Et_3N$, $CH_2Cl_2$, 0°C,

2 hours, 58 (98%), or 59 (96%); (c) for 60: 2.2 equivalents of NaH, 2.2 equivalents of 51, DMF, 25°C, 8 hours, 66%; for 63: 4.0 equivalents of NaH, 1.2 equivalents of 51, DMF, 25°C, 4 hours, 69%; (d) 1.1 equivalents of 53, DMF, 25°C, 4 hours, 73%; for 64: 1.9 equivalents of 53, NMP, 25°C, 99%; (e) for 65: 2.2 equivalents of NaH, 2.5 equivalents of 54, DMF, 25°C, 12 hours, 23%; (f) 1.1 equivalents of 52, DMF, 25°C, 6 hours, 83%; for 66: 2.0 equivalents of 52, DMF, 25°C, 20 hours, 99%; (g) 50% TFA in $CH_2Cl_2$, 25°C, 30 min, 90-99% for 11, 14-19 after RP-HPLC. Boc = tert-butoxycarbonyl; TFA = trifluoroacetic acid; NMP = N-methyl-2-pyrrolidinone; DMF = dimethylformamide.

Figure 9 illustrates the synthesis of compounds 20 and 21 witht the following *Reagents and conditions:* (a) 1.0 equivalent of 55, 2.2 equivalents of $Et_3N$, DMF, 25°C, 16 hours, 92%; (b) 50% TFA in $CH_2Cl_2$, 25°C, 4 hours, 97%; (c) 1.0 equivalent of 56, 2.2 equivalents of $Et_3N$, DMF, 12 hours, 120%(crude yield); (d) 50% TFA in $CH_2Cl_2$, 25°C, 4 hours, 83% after RP-HPLC; TFA = trifluoroacetic acid; DMF = dimethylformamide.

Figure 10 illustrates the synthesis of compound 22 with the following *Reagents and conditions*: (a) $NH_3$, DMF, 25°C, 5 hours, 93%; (b) 10% Pd/C, $H_2$, MeOH, 25°C, 8 hours, 90%; (c) 1.1 equivalent of PhNCS, EtOH, 14 hours, 69%; (d) 1.0 equivalent of $HgCl_2$, 1.0 equivalent of Et3N, DMF, 4 hours, 81%; (e) 50% TFA in CH2Cl2, 30 min, 88% yield, after RP-HPLC. TFA = trifluroacetic acid; DMF = dimethylformamide.

Figure 11 shows a compilation of data which indicates the effect of nitroaryl ethers on RGD-dependent ligand interaction with integrins. The concentration necessary for half-maximal inhibition of ligand binding ($IC_{50}$) is shown. The peptide GRGDSPK and compound 1 were included for reference. The data have been sorted by $IC_{50}$ values(from low to high) on $\alpha_v\beta_3$. The 'cQ' value shows the activity of the NPE relative to the activity of compound 1. The '>', shows that the $IC_{50}$ had not

been reached at the maximum concentration tested, 10 μM.

Figure 12 shows a compilation of data which indicates the effect of nitroaryl ethers on RGD-dependent cell adhesion to immobilized ligands. The concentration necessary for half-maximal inhibition of ligand binding ($IC_{50}$) is shown. 25000 cells were allowed to adhere to immobilized ligands in the presence of the nitroaryl ethers as described herein. The concentration resulting in half-maximal inhibition of cell adhesion ($IC_{50}$) is shown. The data have been sorted by $IC_{50}$ (from low to high) on $\alpha_v\beta_3$ mediated adhesion of M21 cells.

Detailed Description:

Example 1: Design, Synthesis and Biological Evaluation of Nonpeptide Itegrin Antagonists:

In this example we describe the design, chemical synthesis and biological evaluation of a series of nitroaryl-based RGD mimetics. Figure 3 shows the targeted compounds (10-22). Amongst the considerations that led to their design were : (a) the Merck findings pointing to the importance of the guanidine/aryl sulfonamide functionalities (Duggan et al. Abstracts of Papers, 211th ACS National Meeting, New Orleans, LA, March 24-28, 1996; American Chemical Society: Washington, DC, 1996, MEDI 234); and (b) the facile entry into such structures from o-nitro-arylfluorides as shown in Figure 4. The designed molecules fall within the general structure I (Figure 4) which can be derived by coupling the central nitrofluoroaromatic system II with fragments III (nucleophile) and IV (aminoacid component).

For the synthesis of compounds 10-22 (Figure 3), the amino acid derivatives 26, 29a and 29b were required. These intermediates were obtained from L-asparagine (23) as outlined in Figure 5. Thus, conversion of 23 to its Boc derivative

(24, 88%) under standard conditions was followed by benzyl ester formation ($Cs_2CO_3$-BnBr) to afford 25 (88% yield). Reduction of the primary amide with $PhI(OCOCF_3)_2$ furnished derivative 26 in 41% yield. The sulfonamides 29a and 29b were prepared by sulfonylation of the amino group to afford 27a, followed by Hoffmann rearrangement and esterification of the resulting aminoacids (28a and 28b) with isobutylene (Figure 5).

Figure 6 summarizes the initial approach to compounds 10-13. Thus, 4-fluoro-o-nitrobenzoic acid (30) was converted to its methyl ester (31, 98%) by treatment with trimethylorthoacetate at 80°C, and thence reacted with $N_3(CH_2)_2OTBS$ in DMF in the presence of catalytic amounts of TBAF resulting in the formation of compound 32 (73%; yields are unoptimized). Saponification of 32 (LiOH, 99% yield) furnished carboxylic acid 33 which was condensed with building block 26 in the presence of DCC and 4-DMAP to give key intermedate 34 (82% yield). For the synthesis of 10, compound 34 was reduced with $Ph_3P$ in the presence of $H_2O$, to afford amine 35a, together with the rearranged product 35b (80% combined yield) in which the side chain heteratoms have interchanged positions (via an internal nucleophilic attack, see structure 35a). On standing at ambient temperature, primary amine 35a underwent quantitative conversion to primary alcohol 36b. However, it was possible to rapidly manipulate the compound through basic hydrolysis (LiOH) and guanylation (1H-pyrazole-1-carboxamidine•HCl) and obtain the targeted compound 10 albeit in low yield (15% after RP-HPLC purification).

For the synthesis of the sulfonamide compounds 11-13, the common intermediate 34 was deprotected (TFA, 84%) and the liberated amine (37) was reacted with the appropiate sulfonyl chloride to afford compounds 38a (78 %) and 38b (57 %). Reduction of the azide functionality in 38a and 38b with $Ph_3P$-$H_2O$, again resulted in a mixture of the corresponding primary amine (39a and 39b) and its rearranged primary alcohol (41a

and 41b) in 80% total yield. Basic hydrolysis of 39a and 39b resulted in the formation of the corresponding carboxylic acids (40a and 40b, 93-99% yield), guanylation of which as described above furnished the desired compounds 11 and 13 (13-15% yield) respectively. Similarly, hydrolysis of 41a (LiOH, 96% yield) followed by guanylation furnished compound 12 in low yield, via compound 42a.

The rearrangement observed during the reduction of the side chain azido group led us to explore an alternative strategy for the construction of the targeted nitroaryl ether compounds. According to the new plan, a nucleophilic species containing a fully protected guanidine moiety was to be employed in the displacement of the fluoride from the central nitroaryl system. To this end the nucleophiles 51-56 (Poss et al. Tetrahedron Lett. 1992, 33, 5933; Iwanowicz et al. Synth. Commun. 1993, 23, 1443; Cherkaoui et al. Bull. Soc. Chim. Fr. 1991, 255) were prepared from readily available starting materials and by standard chemistry as outlined in Figure 7. The incorporation of these fragments into the mainframe of the molecule via nucleophilic aromatic substitution, and the synthesis of the final targets are shown in Figure 8 (11, 14-19) and Figure 9 (21 and 22). Thus, the acid chloride 57 (derived from carboxylic acid 30) was coupled with amines 29a and 29b in the presence of $Et_3N$ to afford amides 58 (98%) and 59 (99%) respectively. Coupling of 58 with nucleophile 51 was effected in the presence of NaH in DMF to afford product 60 in 66% yield. Similarly 63 was obtained by coupling 59 with 51 (69% yield). The amino compounds 61 and 64 were obtained from 58 and 59 in 73 and 99% yield respectively, by reaction with amine 53 in DMF at ambient temperature. Thioether 62 was obtained by exposure of 58 to thiol 54 and NaH (DMF, 25°C, 23% yield). Treatment of componds 60-64 with TFA in $CH_2Cl_2$ at room temperature resulted in concomitant deprotection of both the guanidine and carboxyl groups in excellent yield (90-99%, after RP-HPLC purification). The piperazine compounds 16 and 19 were prepared in a similar fashion from 58 and 59 respectively by first displacing the fluoride with nucleophile

52, followed by TFA-induced deprotection of the resulting derivatives 65 and 66 as summarized in Figure 8.

The synthesis of compounds 20 and 21 is shown in Figure 9. Thus, reaction of 58 with 55 in the presence of $Et_3N$ at 25°C in DMF resulted in the formation of compound 67 (92% yield) which was exposed to TFA:$CH_2Cl_2$ (1:1) at 25°C to afford targeted benzimidazole 20 (97% yield). In a similar fashion, compound 21 was prepared via the intermediacy of 68 by reaction of 58 with 56 ($Et_3N$, DMF, 25°C, 94%), followed by deprotection (83% after RP-HPLC purification).

Finally, the preparation of compound 22 is shown in Figure 10. Thus, key intermediate 57 was reacted with ammonia in DMF to afford nitroaniline 69 in 93% yield. Reduction of 69 with $H_2$ in the presence of 10% Pd/C catalyst in MeOH led to 1,2 diamine 70 (90%), which reacted with phenylisothiocyanate in EtOH to afford thiourea 71 (69% yield). Treatment of 71 with $HgCl_2$ and $Et_3N$ in DMF at ambient temperature gave guanidine 72 in 81% yield. Cleavage of the tert-butyl ester in 72 with TFA in $CH_2Cl_2$ then led to the targeted compound 22 (80% yield, after RP-HPLC purification).

## EXPERIMENTAL PROTOCALS

General:

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium-benzophenone, and methylene chloride ($CH_2Cl_2$), benzene (PhH), and toluene from calcium hydride. Anhydrous solvents were also obtained by passing them through commercially available activated alumina columns. Yields refer to chromatographically and spectroscopically ($^1H$ NMR) homogeneous materials, unless otherwise stated. All solutions used in workup procedures were saturated unless otherwise noted. All reagents were purchased at highest commercial quality and used without further

purification unless otherwise stated.

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.25, 0.50 or 1 mm E. Merck silica gel plates (60F-254). Reverse phase HPLC was performed on a Waters Model 600E HPLC instrument utilizing a Vydac 218TP1022 column with detection at 254 nm using a 90:10 Æ 40:60 $H_2O$:$CH_3CN$ + 0.1% TFA gradient over 40 minutes.

NMR spectra were recorded on Bruker DRX-600, AMX-500, AMX-400 or AC-250 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; b, broad. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. Electrospray mass spectra were recorded on a Perkin Elmer Science API III mass spectrometer.

**Synthesis of Amino Acid Derivative 25 as shown in Figure 5.**

Compound **25**: To a solution of *t*-butoxy-carbonyl-(*L*)-asparagine **24** (12.6 g, 50 mol; Aldrich) in MeOH (200 mL) was added water (20 mL). The solution was neutralized with a 20% aqueous solution of $Cs_2CO_3$ (57 mL) and then evaporated to dryness. The resulting residue was taken up in DMF (50 mL) and then azeotropically dried by evaporation to dryness. The cesium salt was then taken up in DMF (125 mL) followed by addition of benzyl bromide (6.5 mL, 55 mmol). The mixture was stirred at room temperature for 6 hours, evaporated to dryness

and the residue triturated with water (500 mL). The solid was dissolved in ethyl acetate (150 mL) and the organic phase was washed with water (75 mL), dried over $Na_2SO_4$ and the solvent was removed under reduced pressure. The crude ester was recrystallized from ethyl acetate/hexane to give **25** (15.1 g, 88 %) as a colorless solid. IR (KBr): $n_{max}$ 3401, 3349, 3204, 2982, 2935, 1741, 1688, 1657, 1524, 1293, 1169, 1055 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 7.36-7.32 (m, 5 hours, Ph), 5.73 (d, *J* = 8.5 Hz, 1 H, $NHCO_2$), 5.59 (bs, 1 H, CONH*H*), 5.40 (bs, 1 H, CON*H*H), 5.20 (d, *J* = 12.5 Hz, 1 H, C*H*HPh), 5.17 (d, *J* = 12.5 Hz, 1 H, CH*H*Ph), 4.56 (ddd, *J* = 4.0, 5.0, 8.5 Hz, 1 H, C*H*$CH_2$), 2.95 (dd, *J* = 5.0, 16.5 Hz, 1 H, CHCH*H*), 2.76 (dd, *J* = 4.0, 16.5 Hz, 1 H, CHC*H*H), 1.42 (s, 9 H, $^t$Bu); $^{13}C$ NMR (150 MHz, $CDCl_3$): d 171.9, 171.2, 155.7, 135.4, 128.5, 128.3, 128.2, 80.1, 67.4, 50.3, 37.4, 28.3; FAB-HRMS ($M+Na^+$) calcd 345.1426, found 345.1421.

**Synthesis of compound 26 as illustrated in Figure 5**: To a stirred solution of bis[trifluoroacetoxy]phenyl iodine (2.0 g, 4.7 mmol) in DMF:$H_2O$ (24 mL, 1:1, v/v) compound **25** (1.0 gram, 3.1 mmol) was added at room temperature. After 15 min, pyridine (0.5 mL, 6.2 mmol) was added and stirring was continued for 3 hours. The solvent was removed under reduced pressure and the residue dissolved in water (30 mL). The solution was washed with ether and the aqueous layer was basified with 1 N NaOH and extracted with dichloromethane. The solvent was removed under reduced pressure to give an oily residue. Purification by flash column chromatography (10 % MeOH in $CH_2Cl_2$) gave amine **26** as a yellow oil (0.37 grams, 41%). $R_f$ = 0.11 (2.5% methanol in ethyl acetate); IR (thin film): $n_{max}$ 3366, 3313, 3064, 2979, 2934, 1688, 1518, 1501, 1456, 1393, 1368, 1324, 1254, 1204, 1166, 1055, 1002, 838, 800, 743, 692 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 7.36-7.28 (m, 5 H, Ph), 6.36 (bm, 2 H, $NH_2$), 6.06 (d, *J* = 7.5 Hz, 1 H, $NHCO_2$), 5.18 (d, *J* = 12.0 Hz, 1 H, C*H*HPh), 5.13 (d, *J* = 12.0 Hz, 1 H, CH*H*Ph), 4.52-4.43 (bm, 1 H, C*H*$CH_2$), 3.35 (bdd, *J* = 12.5 Hz, 1 H, CHC*H*H), 3.24 (bdd, *J* = 6.5, 12.5 Hz, 1 H, CHC*H*H), 1.32 (s,

9 H, $^t$Bu); $^{13}$C NMR (125 MHz, $CDCl_3$): d 170.0, 155.9, 134.8, 128.5, 128.4, 128.3, 80.6, 67.7, 52.9, 41.6, 28.0; FAB-HRMS ($M+H^+$) calcd 295.1658, found 295.1650.

**Synthesis of compound 27a as illustrated in Figure 5**. To a solution of (*L*)-asparagine (**23**) (10.00 grams, 75.7 mmol) in $H_2O$:dioxane (50 mL:50 mL) was added NaOH (3.40 grams, 85.0 mmol) at 0°C. After 15 min at 0°C, phenylsulfonylchloride (10.6 mL, 84.0 mmol) was added followed by addition of a solution of NaOH (3.40 grams, 85.0 mmol) in $H_2O$ (50 mL) at 0°C. After 30 min the cooling bath was removed and the solution was concentrated to ca. 50 mL under reduced pressure. The aqueous phase was extracted with ethyl acetate (2 x 50 mL). The aqueous layer was acidified at 0°C with conc. aqueous HCl (pH ≈ 1) while the protected amino acid precipitated. The resulting solid was collected by filtration and washed with $H_2O$ (20 mL). Overnight drying in an oven at ca. 50°C gave **27a** as a colorless solid (14.6 grams, 71%). The crude product was used without further purification. IR (KBr): $n_{max}$ 3495, 3338, 3260, 1723, 1648, 1578, 1449, 1325, 1261, 1202, 1166, 1086 $cm^{-1}$; $^1$H NMR (500 MHz, methanol-$d^4$): d 7.88-7.86 (m, 2 H, Ph), 7.60-7.57 (m, 1 H, Ph), 7.54-7.51 (m, 2 H, Ph), 4.23 (t, 1 H, *J* = 6.0 Hz, C*H*$CO_2$H), 2.66 (dd, 1 H, *J* = 6.0, 15.5 Hz, C*H*H(C=O)$NH_2$), 2.60 (dd, *J* =6.0, 15.5 Hz, CH*H*(C=O)$NH_2$); $^{13}$C NMR (125 MHz, methanol-$d^4$): d 174.3, 173.6, 142.1, 133.7, 130.0, 128.2, 53.9, 39.6; FAB-HRMS ($M+H^+$) calcd 273.0545, found 273.0540.

**Synthesis of compound 27b as shown in Figure 5**. Compound **27b** was prepared by the same procedure as for **27a** using 2-naphthalenesulfonlyl chloride in lieu of phenylsulfonylchloride. Crude yield: 16.06 g (66%). IR (KBr): $n_{max}$ 3424, 3289, 2925, 1851, 1713, 1673, 1502, 1399, 1333, 1258, 1223, 1191, 1159, 1127, 1075, 1023, 964, 866, 822, 794, 714, 669, 638, 548, 477 $cm^{-1}$; $^1$H NMR (500 MHz, DMSO-$d^6$): d 8.40 (d, *J* = 1.0 Hz, 1 H, naphthyl), 8.15 (d, *J* = 9.0 Hz, 1 H, $NHSO_2$), 8.12 (d, *J* = 8.0 Hz, 1 H, naphthyl), 8.07 (d, *J* = 9.0

Hz, 1 H, naphthyl), 8.01 (d, *J* = 8.0 Hz, 1 H, naphthyl), 7.81 (dd, *J* = 1.5, 8.8 Hz, 1 H, naphthyl), 7.68 (ddd, *J* = 1.5, 6.8, 7.5 Hz, 1 H, naphthyl), 7.64 (ddd, *J* = 1.5, 6.8, 7.5 Hz, 1 H, naphthyl), 7.33 (bs, 1 H, CONH*H*), 6.87 (bs, 1 H, CON*H*H), 4.16 (bm, 1 H, C*H*$CH_2$), 2.47 (dd, *J* = 7.0, 15.5 Hz, 1 H, CHCH*H*) 2.28 (dd, *J* = 6.5, 15.5 Hz, 1 H, CHC*H*H); $^{13}$C NMR (125 MHz, DMSO-$d^6$): d 172.0, 170.5, 138.4, 134.1, 131.6, 129.2, 129.0, 128.6, 127.8, 127.4, 127.1, 122.6, 52.5, 38.0; FAB-HRMS (M+H') calcd 323.0702, found 323.0708.

**Synthesis of compound 55(b) wherein -$NH_2$ substituent of compound 55 is replaced with -OH.**

Step A: To a solution of 3-hydroxypropionic acid (.073 g, 0.16 mmol, 1.0 equiv.) was added DMF (0.5 mL, .32 M), imidazole (26.0 mg, 0.38 mmol, 2.4 equiv.) and TBDPSCl (.046 mL, 0.19 mmol, 1.2 equiv.) and allowed to stir for 2.5 hour at 25 °C. The solution was then diluted with ether (10 mL) and then washed with a saturated solution of 5% hydrogen chloride (2X 10 mL), water (2X 10 mL), brine (1X 5 mL) and then dried over $MgSO_4$. The compound was purified by flash column chromatography (silica, 80% ether in light petroleum ether) and carried onto the next step as follows:

Step B: To a solution of phenylenediamine (1.08 g, 0.01 mol) in 5.5 N HCl (10 mL) was added the protected intermediate formed in step A (1.125g, 0.015 mol) at room temperature. The reaction mixture was refluxed for 24 h and then allowed to cool to room temperature. The solvent was removed *in vacuo* to give a precipitate, which was filtered and washed with ether; and then

Step C: The TBDPS group was removed as follows: A solution of intermediate from Step B (7.481 mmol) in THF (0.1M) was cooled to 0 °C and treated with azeotropically dried (benzene, 3 x 50 mL) TBAF (22.44 mmol). The reaction mixture was stirred at 0 °C for 10 h and quenched with saturated aqueous $NH_4Cl$. the two layers were separated and the aqueous phase was extracted with a mixture of ethyl

acetate and ethyl ether. The combined organic phase was washed with brine, dried, and concentrated. Purification by silica gel column chromatography gave the pure compound 55(b) wherein $-NH_2$ substituent of compound 55 is replaced with -OH.

**Synthesis of compound 55(c) wherein $-NH_2$ substituent of compound 55 is replaced with -SH.**

To a solution of phenylenediamine (1.08 g, 0.01 mol) in 5.5 N HCl (10 mL) was added 3-mercaptopropionic acid (1.125g, 0.015 mol) at room temperature. The reaction mixture was refluxed for 24 h and then allowed to cool to room temperature. The solvent was removed *in vacuo* to give a precipitate, which was filtered and washed with ether to give the pure compound 55(c) wherein $-NH_2$ substituent of compound 55 is replaced with -SH.

**Synthesis of compound 67 (b) and (c) wherein the -NH- group is substituted by either an -S- or -O- diradical (-NH- case is illustrated in Figure 9).** To a solution of **57** (0.10 g, 0.20 mmol; synthesized above) in DMF (8 mL) was added **55 (b) or (c)** (0.038 g, 0.22 mmol; synthesized above) and triethylamine (0.06 mL, 0.44 mmol) at room temperature. After stirring at 25 °C for 16 h, the reaction mixture was diluted with EtOAc (10 mL) and water (10 mL). The layers were seperated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic extracts were collected and washed with water (2 x 10 mL) and brine (20 mL) and dried over $Na_2SO_4$. After filtration and evaporation under reduced pressure the residue was purified by flash chromatography (silica, ethyl acetate) to give **67 (b) or (c)**.

**Synthesis of compound 20 (b) or (c) wherein the -NH group is substituted by either an -S- or -O- diradical (-NH- case is illustrated in Figure 9).** To a solution of **67 (b) or (c)** (0.068 g, 0.11 mmol; synthesized above) in $CH_2Cl_2$ (2 mL) was added trifluoroacetic acid (2 mL) at room temperature. After

4 h, the solvent was removed *in vacuo* to give an oil which after RP-HPLC (C-18) gave **20 (b) or (c)** as a yellow solid.

**Synthesis of compound 28a as illustrated in Figure 5**. To a round-bottom flask equipped with a magnetic stirring bar was added an aqueous solution of NaOH (11.15 grams, 280.0 mmol) in water (50 mL) and cooled to 0°C. Bromine (2.60 mL, 50.0 mmol) was added dropwise within 5 min and the reaction mixture was stirred for further 5 min at this temperature. A solution of the protected amino acid **27a** (10.44 grams, 38.0 mmol) in a solution of NaOH (3.10 grams, 70.0 mmol, 30 mL $H_2O$) was added in one portion at 0°C. Stirring was continued at this temperature for 20 min and upon removal of the cooling bath the reaction mixture was heated to 90°C for an additional 30 min. After cooling to 0°C the pH of the reaction mixture was adjusted to 7 with concentrated and 1 M aqueous HCl. The resulting colourless precipitate was collected by filtration. The residue was washed with water, dried overnight in an oven at ca. 50°C to give **28a** as colorless solid (6.95 grams, 75%). The crude product was used without further purification. IR (KBr): $n_{max}$ 3509, 3299, 3058, 2936, 1636, 1596, 1522, 1446, 1413, 1355, 1340, 1300, 1246, 1163, 1094, 1028, 924 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d^6$): d 7.84-7.82 (m, 2 H, Ph), 7.66-7.63 (m, 1 H, Ph), 7.60-7.56 (m, 2 H, Ph), 7.58 (bm, 1 H, $NHSO_2Ph$), 3.35 (bs, 2 H, $NH_2$), 3.17 (dd, *J* = 4.5, 9.5 Hz, 1 H, C*H*$CH_2$), 3.01 (dd, *J* = 2.5, 12.0 Hz, 1 H, C*H*H), 2.80 (dd, *J* = 9.5, 12.0 Hz, 1 H, CH*H*); $^{13}C$ NMR (125 MHz, DMSO-$d^6$): d 169.4, 139.1, 132.7, 129.2, 126.8, 52.7, 41.7; FAB-HRMS ($M+Na^+$) calcd 245.0596, found 245.0599.

**Synthesis of compound 28b as illustrated in Figure 5**. Compound **28b** was prepared by the same procedure as for **28a** using 27b instead of 27a. Crude yield: (11.88 grams, 81 %) as a beige-coloured solid. IR (KBr): $n_{max}$ 3338, 3241, 3056, 2831, 2601, 1651, 1604, 1513, 1463, 1404, 1382, 1335, 1151, 1076, 1039, 985, 955, 931, 913, 855, 814, 787, 749, 657, 618, 550, 480

$cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d^6$): d 8.48 (br. s, 1 H, naphthyl), 8.16-8.10 (2 bd, 2 H, naphthyl), 8.04 (d, $J$ = 8.5 Hz, 1 H, naphthyl), 7.85 (dd, $J$ = 2.0, 8.5 Hz, 1 H, naphthyl), 7.70 (ddd, $J$ = 1.5, 7.0, 8.0 Hz, 1 H, naphthyl), 7.66 (ddd, $J$ = 1.0, 7.0, 8.0 Hz, 1 H, naphthyl), 7.45 (bm, 1 H, $NHSO_2$), 3.54-3.19 (bm, 2 H, $NH_2$), 3.23 (dd, superimposed, $J$ = 4.5, 9.5 Hz, 1 H, C*H*$CH_2$), 3.04 (dd, $J$ = 4.5, 12.00 Hz, 1 H, CHC*H*H), 2.83 (dd, $J$ = 9.5, 12.00 Hz, 1 H, CHCH*H*); $^{13}C$ NMR (125 MHz, DMSO-$d^6$): d 169.3, 136.1, 134.3, 131.6, 129.4, 129.2, 128.9, 128.0, 127.8, 127.6, 122.5, 52.7, 41.6; FAB-HRMS ($M+H^+$) calcd 295.0753, found 295.0761.

**Synthesis of compound 29a as illustrated in Figure 5**. A sealed tube equipped with a magnetic stirring bar was charged with **28a** (4.88 grams, 20.0 mmol) and 75 mL of anhydrous dimethoxyethane. After addition of 3.0 mL of conc. $H_2SO_4$ the reaction mixture was cooled to -78°C under an atmosphere of argon and 40.0 mL of isobutylene was condensed into the sealed tube. After sealing the cooling bath was removed and the reaction mixture was stirred for 48 hours at room temperature. The reaction mixture was poured into 100 mL of ice water. The aqueous solution was extracted with diethyl ether (40 mL) and then the pH of the aqueous phase adjusted to 12-13 with 6 N aqueous NaOH. The free amine was extracted with ethyl acetate (4 x 50 mL) and the combined organic extracts were washed succesively with saturated aqueous $NaHCO_3$-solution (50 mL), 5 % aqueous $KHSO_4$-solution (50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$, filtrated and the solvent removed in vacuo to give **29a** (10.9 grams, 55.5%) as an off-white solid. The crude product was used without further purification. $R_f$ = 0.27 (silica gel, ethyl acetate); IR (KBr) $n_{max}$ 3372, 3295, 2981, 2932, 1726, 1452, 1337, 1261, 1161, 1094, 945, 898, 845, 753 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 7.86-7.84 (m, 2 H, Ph), 7.58-7.54 (m, 1 H, Ph), 7.51-7.48 (m, 1 H, Ph), 3.76 (dd, $J$ = 4.0, 5.5 Hz, 1 H, C*H*$CH_2$), 3.02 (dd, $J$ = 9.0, 13.0 Hz, 1 H, C*H*H), 2.88 (dd, $J$ = 5.5, 13.0 Hz, 1 H, CH*H*), 1.27 (s, 9 H, $^t$Bu); $^{13}C$ NMR (125 MHz, $CDCl_3$): d 169.3,

139.7, 132.8, 129.1, 127.2, 82.8, 58.8, 44.9, 27.7; FAB-HRMS ($M+H^+$) calcd 301.1222, found 301.1211.

**Synthesis of 29b as illustrated in Figure 5**. Compound **29b** was prepared by the same procedure as for **29a** using **28b** instead of **28a**. Crude yield: 4.56 g (51%) as an off-white solid. $R_f$ = 0.25 (silica gel, ethyl acetate + 2 % v/v $Et_3N$); IR (KBr): $n_{max}$ 3360, 3264, 3057, 2981, 2935, 2873, 2747, 1731, 1588, 1501, 1455, 1339, 1254, 1220, 1157, 1076, 952, 926, 823, 782, 747, 663, 619, 552, 481 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 8.40 (bs, 1 H, naphthyl), 7.92 (bd, $J$ = 8.5 Hz, 2H, naphthyl), 7.86 (d, $J$ = 8.0 Hz, 1H, naphthyl), 7.82 (dd, $J$ = 1.5, 8.5 Hz, 1 H, naphthyl), 7.64-7.55 (2 x ddd, superimposed, $J$ = 1.0, 7.0, 8.5 Hz, 2 H, naphthyl), 3.84 (dd, $J$ = 4.2, 5.8 Hz, 1 H, C*H*$CH_2$), 3.30-2.60 (bm, superimposed, 2 H, $NH_2$), 3.03 (dd, $J$ = 4.2, 13.4 Hz, 1 H, CHC*H*H), 2.88 (dd, $J$ = 5.8, 13.4 Hz, 1 H, CHCH*H*), 1.08 (s, 9 H, *t*-Bu); $^{13}C$ NMR (125 MHz, $CDCl_3$): d 169.2, 136.3, 134.9, 132.0, 129.5, 129.2, 128.9, 128.6, 127.8, 127.5, 122.4, 82.9, 58.6, 44.6, 27.5; FAB-HRMS ($M+H^+$) calcd 351.1379, found 351.1371.

**Synthesis of compound 31 as illustrated in Figure 6**. To a suspension of the acid **30** (5.0 grams, 27 mmol; Aldrich) in toluene was added trimethylorthoacetate (17 mL, 135 mmol). The mixture was heated to 80 °C for 12 hours and the solvent removed under reduced pressure to give **31** as a colorless solid (5.26 grams, 98%). $R_f$ = 0.46 (silica gel, 25% ethyl acetate in hexane); IR (KBr): $n_{max}$ 3061, 2960, 1714, 1614, 1542, 1438, 1351, 1297, 1262, 1233, 1130, 871, 755 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 8.74 (dd, $J$ = $^4J$ ($^1H$-$^1H$) = 2.0 Hz, $^4J$ ($^1H$-$^{19}F$) = 7.0 Hz, 1 H, 2-Ar-H), 8.32 (ddd, $^4J$($^1H$-$^1H$) = 2.0 Hz, $^4J$ ($^1H$-$^{19}F$) = 4.5 Hz, $^3J$ ($^1H$-$^1H$) = 9.0, 1 H, 6-Ar-H), 7.39 (dd, $^3J$ ($^1H$-$^1H$) = 9.0 Hz, $^3J$ ($^1H$-$^{19}F$) = 10.5 Hz, 1 H, 5-Ar-H); $^{13}C$ NMR (125 MHz, $CDCl_3$): d 164.1, 159.1, 156.9, 136.5, 127.8, 118.8, 118.7, 52.9; FAB-HRMS ($M+H^+$) calcd 200.0281, found 200.0286.

**Synthesis of compound 32 as illustrated in Figure 6**. To a

solution of **31** (4.0 grams, 20 mmol) in DMF (10 mL) were added *ca.* 4 g of 4 Å molecular sieves and 4.46 g (0.22 mmol) of $N_3(CH_2)_2OTBS$ at room temperature. After 10 min 2 mL (2.0 mmol) of a 1 M solution of TBAF in THF was added. The mixture was stirred for 4 hours at room temperatutre and then filtered through a short path of celite®. The filtrate was taken up in ethyl acetate (100 mL) and successively washed with water, saturated aqueous $NaHCO_3$-solution and brine. The organic extract was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a yellow oil. Flash column chromatography (silica gel, 40% ethyl acetate in hexanes) gave **32** as a yellow solid (3.85 grams, 73%). $R_f$ = 0.35 (silica gel, 40% ethyl acetate in hexanes); IR (KBr): $n_{max}$ 2950, 2938, 2114, 1713, 1620, 1536, 1438, 1349, 1303, 1276, 1247, 1161, 1136, 918, 760 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 8.54 (d, *J* = 2.0 Hz, 1 H, Ar), 8.22 (dd, *J* = 2.0, 9.0 Hz, 1 H, Ar), 7.13 (d, *J* = 9.0 Hz, 1 H, Ar), 4.32 (t, *J* = 5.0 Hz, 2 H, $OCH_2$), 3.94 (s, 3 H, $OCH_3$), 3.71 (t, *J* = 5.0 Hz, 2 H, $CH_2N_3$); $^{13}C$ NMR (125 MHz, $CDCl_3$): d 164.7, 154.7, 135.3, 127.3, 123.3, 114.0, 68.8, 52.5, 49.7; FAB-HRMS (M+Na$^+$) calcd 289.0549, found 289.0553.

**Synthesis of compound 33 as illustrated in Figure 6**. To a solution of **32** (3.85 grams, 14.0 mmol) in 1,4-dioxane:water (90 mL:30 mL) was added $LiOH \bullet H_2O$ (1.2 grams, 28 mmol). The reaction mixture was stirred at room temperature for 4 hours and then 40 mL of a saturated aqueous $NH_4Cl$-solution was added. The organic solvent was removed under reduced pressure to give a yellow slush. The slush was taken up in water and acidified with aqueous 1M $KHSO_4$-solution. The aqueous layer was then extracted with $CH_2Cl_2$ (3 x 70 ml). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give **33** as a yellow solid (3.50 grams, 99%). $R_f$ = 0.10 (silica gel, 60 % ethyl acetate in hexanes); IR (KBr): $n_{max}$ 3087, 2964, 2877, 2659, 2539, 2120, 1699, 1616, 1534, 1429, 1359, 1282, 1163, 1138, 1079, 1039, 1002, 929, 847, 763, 687, 642, 546 $cm^{-1}$; $^1H$ NMR (500 MHz, methanol-$d^4$): d 8.40 (d, *J* = 2.0 Hz, 1 H, Ar), 8.22

(dd, $J$ = 2.0, 9.0 Hz, 1 H, Ar), 7.37 (d, $J$ = 9.0 Hz, 1 H, Ar), 4.37 (t, $J$ = 4.5 Hz, 2 H, $OCH_2$), 3.67 (t, $J$ = 5.0 Hz, 2 H, $CH_2N_3$); $^{13}C$ NMR (125 MHz, methanol-d$^4$): d 167.4, 156.0, 140.9, 136.4, 127.9, 124.9, 115.7, 70.3, 51.1; FAB-HRMS (M+Na$^+$) calcd 275.0392, found 275.0395.

**Synthesis of compound 34 as illustrated in Figure 6**. To a solution of amine **26** (0.33 grams, 1.10 mmol) and acid **33** (0.286 grams, 1.10 mmol) in $CH_2Cl_2$ (30 mL) was added a catalytic amount of DMAP (0.03 grams, 0.22 mol) and DCC (0.26 grams, 1.1 mol) at room temperature. The reaction mixture was stirred for 4 hours at this temperature and the precipated dicyclohexyl urea was then filtered and the filtrate washed successively with water, saturated aqueous $NaHCO_3$-solution and brine. The organic solvent was removed under reduced pressure to give an oil which after purification by flash column chromatography (silica gel, 60% ethyl acetate in hexanes) gave amide **34** as a yellow solid (2.48 grams, 82%). $R_f$ = 0.28 (silica gel, 60% ethyl acetate in hexanes); IR (KBr): $n_{max}$ 3343, 2977, 2933, 2112, 1738, 1710, 1619, 1531, 1498, 1366, 1333, 1280, 1161, 1084, 1047 cm$^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 8.23 (d, $J$ = 2.0 Hz, 1 H, Ar), 7.98 (dd, $J$ = 2.0, 11.0 Hz, 1 H, Ar), 7.40 (bt, 1 H, NHCO), 7.39-7.31 (m, 5 H, Ph), 7.09 (d, $J$ = 11.0 Hz, 1 H, Ar), 5.67 (d, $J$ = 8.0 Hz, 1 H, $NHCO_2$), 5.21 (s, 2 H, $CH_2Ph$), 4.60-4.50 (bm, 1 H, C*H*$CH_2$), 4.30 (t, $J$ = 6.0 Hz, 2 H, $OCH_2$), 3.95-3.85 (bm, 1 H, CHC*H*H), 3.78-3.70 (bm, superimposed, 1 H, CHCH*H*), 3.70 (t, $J$ = 6.0 Hz, 2 H, $CH_2N_3$), 1.43 (s, 9 H, $^t$Bu); $^{13}C$ NMR (125 MHz, $CDCl_3$): d 170.0, 164.9, 153.8, 139.8, 135.0, 133.0, 128.7, 128.6, 126.9, 124.6, 114.3, 81.0, 68.8, 67.9, 49.8, 33.8, 28.2, 25.5, 24.8; FAB-HRMS (M+Cs$^+$) calcd 661.1023, found 661.1050.

**Synthesis of compounds 35ab as illustrated in Figure 6**. To a solution of the azide **34** (50 mg, 0.095 mmol) in a mixture of THF:$H_2O$ (8 mL THF: 0.04 mL $H_2O$) was added triphenylphosphine (50 mg, 0.19 mmol). The reaction mixture was stirred at room temperature for 14 hours and the solvent was removed under

reduced pressure. Purification of the crude residue by flash column chromatography (silica gel, 20 % methanol in dichloromethane) gave two major fractions (total yield 80 %). Fraction 1: 17 mg (yellowish oil, 40 %), fraction 2: 17 mg (yellowish oil, 40 %). Fraction 1 was positive in ninhydrin test while fraction 2 was negative. Fraction 1 **35a** $R_f$ = 0.48 (silica gel, 20 % methanol in dichloromethane); $^1$H NMR (500 MHz, $CDCl_3$): d 8.22 (m, 1 H, Ar), 7.94 (d, *J* = 9.0 Hz, 1 H, Ar), 7.43-7.30 (m, 6 H), 7.07 (d, *J* = 9.0 Hz, 1 H, Ar), 5.80 (d, *J* = 6.0 Hz, 1 H, N*H*Boc), 5.19 (s, 2 H, C$H_2$Ph), 4.54 (bm, 1 H, C*H*NHBoc), 4.21 (bm, 2 H, C$H_2$OAr), 3.87-3.76 (m, 2 H), 3.19 (s, 2 H, C$H_2$NH$_2$), 2.75 (bs, 2 H, N$H_2$), 1.41 (s, 9 H, $^t$Bu); FAB-HRMS (M+H$^+$) calcd 503.2142, found 503.2162. Fraction 2 **35b**: $R_f$ = 0.86 (silica gel, 20 % methanol in dichloromethane); $^1$H NMR (500 MHz, $CDCl_3$): d = 8.46 (m, 1 H, Ar), 8.42 (t, *J* =6.5 Hz, 1 H, N*H*Ar), 7.79 (dd, *J* = 2.5, 11.0 Hz, 1 H, Ar), 7.38-7.28 (m, 5 H, Ar), 7.21 (m, 1 H, N*H*CO), 6.80 (d, *J* = 11.0 Hz, 1 H, Ar), 5.85 (d, *J* = 9.0 Hz, 1 H, N*H*Boc), 5.19 (s, 2 H, C$H_2$Ph), 4.53 (m, 1 H, C*H*NHBoc), 3.92 (t, *J* = 6.5 Hz, 2 H, C$H_2$OH), 3.88-3.73 (m, 2 H, C$H_2$NH(CO)), 3.52-3.38 (m, 2 H, C$H_2$NHAr), 1.41(s, 9 H, $^t$Bu); FAB-HRMS (M+Cs$^+$) calcd 635.118, found 635.110.

**Synthesis of compound 10 as illustrated in Figure 6**. To a solution of **35a** (0.023g, 0.046 mmol) in a mixture of THF:$H_2O$ (6 mL:2 mL) was added LiOH•$H_2O$ (4 mg, 0.092 mmol) at room temperature. The mixture was stirred for 4 hours and then acidified with acetic acid. The solvent was removed under reduced pressure and the residue used in the next step without further purification. To a solution of the crude acid in 2 ml of anhydrous DMF was added *N, N*-diisopropylethylamine (9 mL, 0.05 mmol) and 1*H*-pyrazole carboxamidine•HCl (8 mg, 0.05mmol). After 16 hours, the solvent was removed under reduced pressure and the residue was purified by RP-HPLC (C-18) to give **10** (3.25 mg, 13%) as a yellowish solid. $R_t$ = 20.5 min; $^1$H NMR (500 MHz, $D_2O$): d 8.33 (d, 1 H, *J* = 2.0 Hz, Ar), 7.98 (dd, 1 H, *J* = 2.0, 9.0 Hz, Ar), 7.30 (d, *J* = 9.0 Hz, 1 H, Ar), 4.42 (m, 1 H,

C*H*NHBoc), 4.34 (t, J = 4.0 Hz, 2 H, C$H_2$NH(CO)), 3.82 (m, 2 H, $NH_2$(C=NH)NHC$H_2$, 3.63 (t, 2 H, *J* = 4.0 Hz, 2 H, C$H_2$O); FAB-HRMS (M+$Cs^+$) calcd 587.0866, found 587.0895.

**Synthesis of compound 37 as illustrated in Figure 6.** To a solution of **34** (0.10 grams, 0.019 mmol) in $CH_2Cl_2$ (4 mL) at room temperature was added trifluoroacetic acid (4 mL). The mixture was stirred for 2 hours. The solvent was removed *in vacuo* to give a yellowish oil, which after flash chromatography (silica, 5% methanol in dichloromethane) gave **37** as an oil (0.07 grams, 84%). $R_f$ = 0.19 (silica, 5% methanol in dichloromethane); $^1$H NMR (500 MHz, $CDCl_3$): d 8.21 (d, *J* = 2.0 Hz, 1 H, 2-Ar-H), 7.95 (dd, *J* =2.0, 11.0 Hz, 1 H, 6-Ar-H), 7.39-7.29 (m, 5 H, Ar), 7.21 (bm, 1 H), 7.05 (d, *J* = 9.0 Hz, 1 H), 5.16 (s, 2 H, $CH_2$Ph), 4.27 (t, *J* = 5.0 Hz, 2 H, C$H_2$OAr), 3.67 (t, *J* = 5.0 Hz, 2 H, C$H_2N_3$), 3.95-3.78 (bm, 1 H, C*H*$NH_2$), 3.65-3.52 (bm, 1 H, CHC*H*H), 4.32-4.31 (bm, 1 H, CHCH*H*); $^{13}$C (125 MHz, $CDCl_3$): d 164.9, 153.7, 139.2, 135.1, 133.1, 128.6, 128.5, 128.4, 127.0, 124.6, 114.2, 68.7, 67.4, 49.7, 33.8, 25.5; FAB-HRMS (M+$Cs^+$) calcd 561.0499, found 561.0507.

**Synthesis of compound 38a as illustrated in Figure 6.** To a solution of **37** (0.13 grams, 0.30 mmol) in $CH_2Cl_2$ (10 mL) was added *N*, *N*-diisopropylethylamine (0.07 mL, 0.39 mmol) and benzenesulfonyl chloride (0.034 mL, 0.33 mmol) at room temperature. After 4 hours, the reaction mixture was diluted with $CH_2Cl_2$ (10 mL) and water (10 mL). The layers were seperated and the organic layer washed with a saturated solution of sodium bicarbonate and brine and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, which after preparative thin layer chromatography (silica, 60% ether in hexanes) gave **38a** as an oil (0.13 grams, 78%). $R_f$ = 0.43 (silica, 60% ether in hexane); $^1$H NMR (500 MHz,$CDCl_3$): d 8.26 (d, *J* = 2.0 Hz, 1 H, 2-Ar-H), 7.98 (dd, *J* = 2.0, 9.0 Hz, 1 H, 6-Ar-H), 7.81 (d, *J* = 8.0 Hz, 2 H, Ar), 7.53 (t, *J* = 8.0 Hz, 1 H, *p*-phenyl), 7.42 (t, *J* = 8.0 Hz, 2 H, *m*-phenyl), 7.31-7.30

(m, 3 H, Ar), 7.22-7.21 (m, 2 H, Ar), 7.08 (d, *J* = 9.0 Hz, 1 H, 5-Ar-H), 7.03 (t, J =5.5 Hz, 1 H), 5.03 (d, *J* = 12.0 Hz, 1 H, PhC*H*H), 4.99 (d, *J* = 12.0 Hz, 1 H, PhCH*H*), 4.29 (t, *J* = 4.5 Hz, 2 H, $CH_2O$), 4.16 (dd, *J* = 4.0, 7.5 Hz, 1 H, CHC*H*H), 3.92-3.87 (m, 1 H, C*H*$CH_2$), 3.72-3.67 (m, superimposed, 3 H , CHCH*H*, $CH_2N_3$) ; $^{13}C$ NMR (125 MHz, $CDCl_3$): d 169.2, 165.2, 153.7, 139.3, 138.7, 134.3, 133.1, 132.9, 129.1, 128.4, 128.3, 126.9, 126.5, 124.9, 114.1, 68.7, 68.1, 55.4, 49.7, 42.4 ; FAB-HRMS ($M+Cs^+$) calcd 701.0431, found 701.0442.

**Synthesis of compound 38b as shown in Figure 6**. Compound **38b** was prepared by the same procedure as for **38a** using 1-Naphthalene sulfonyl chloride in lieu of phenyl sulfonyl chloride. Yield: (0.031g, 57%) as an oil. $R_f$ = 0.18 (5% methanol in dichloromethane); IR (thin film): $n_{max}$ 3277, 2930, 2112, 1740, 1652, 1618, 1523, 1496, 1348, 1280, 1162, 1125, 984, 910, 772 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): d 8.60 (d, *J* = 11.0 Hz, 1 H, naphthyl), 8.21 (dd, *J* = 2.0, 9.3 Hz, 1 H, naphthyl), 8.03 (d, *J* = 2.9 Hz, 1 H, 2-Ar-H), 8.01 (d, *J* = 10.4 Hz, 1 H, naphthyl), 7.87 (d, *J* = 9.3 Hz, 1 H, naphthyl), 7.81 (dd, *J* = 2.9, 11.0 Hz, 1 H, 6-Ar-H), 7.62 (ddd, *J* = 1.7, 8.7, 8.7 Hz, 1 H, naphthyl), 7.54 (ddd, *J* = 1.3, 8.8, 8.8 Hz, 1 H, naphthyl), 7.47 (dd, *J* = 9.4, 10.1 Hz, 1 H, naphthyl), 7.28-7.22 (m, 3 H, Ph), 7.12-7.07 (m, 2 H, Ph), 6.98 (d, *J* = 11.0 Hz, 1 H, 5-Ar-H), 6.69 (dd, *J* = 7.5 Hz, 1 H, NHCO), 6.22 (d, *J* = 9.5 Hz, 1 H, $NHSO_2$), 4.89 (d, *J* = 15.0 Hz, 1 H, C*H*HPh), 4.83 (d, *J* = 15 Hz, 1H, CH*H*Ph), 4.25 (t, *J* = 6.0 Hz, 2 H, $OCH_2$), 4.13 (ddd, *J* = 5.4, 9.4, 9.5 Hz, 1 H, C*H*$CH_2$), 3.74 (ddd, *J* = 5.4, 7.4, 17.5 Hz, 1 H, CHC*H*H), 3.69 (t, *J* = 6.1 Hz, 2 H, $CH_2N_3$), 3.67 (ddd, superimposed, *J* = 7.5, 9.0, 17.5 Hz, 1 H, CHCH*H*); $^{13}C$ NMR (125 MHz, $CDCl_3$): d 169.3, 165.1, 153.7, 139.1, 134.8, 134.4, 134.0, 133.5, 132.9, 129.9, 129.0, 128.6, 128.5, 128.3, 127.7, 126.3, 124.8, 124.1, 114.0, 68.7, 67.9, 55.7, 49.8, 42.2; FAB-HRMS($M+Cs^+$) calcd 751.0587, found 751.0599.

**Synthesis of compounds 39a and 41a as illustrated in Figure 6**. Compounds **39a** and **41a** were prepared by the same

procedure as for **35ab** using compound 38b in lieu of 38a. Yield: (F1 = 0.029 grams, F2 = 0.028 g), total yield (80%). F2 was positive in ninhydrin test while F1 was not. $R_f$ (F1) **41a** = 0.39 (silica, 10% methanol in dichloromethane); $^1$H NMR (500 MHz, $CDCl_3$): d 8.35 (bs, 1 H, 2-Ar-H), 8.31 (bs, 1 H, $CH_2NHAr$), 7.76-7.60 (m, superimposed, 3 H, Ar), 7.50 (bs, 1 H), 7.38 (t, $J$ = 9.0 Hz, 1 H, Ar), 7.28 (t, $J$ = 9.0 Hz, 2 H, Ar), 7.26-7.13 (m, 5 H, Ar), 6.86 (d, $J$ = 11.0 Hz, 1 H, Ar), 6.64 (d, $J$ = 11.0 Hz, 1 H, $NHSO_2$), 4.92 (d, $J$ = 15.0 Hz, 1 H, PhC*H*H), 4.86 (d, $J$ = 15.0 Hz, 1 H, PhCH*H*), 4.26-4.23 (m, 1 H, $CHCH_2$), 3.80-3.67 (m, superimposed, 4 H, $HOCH_2$, $CHCH_2$), 3.34-3.31 (bm, $CH_2NHAr$), 2.92 (bs, $CH_2OH$) ; $R_f$ (F2) **39a** = 0.16 (silica, 20 % methanol in dichloromethane); $^1$H NMR (500 MHz, $CDCl_3$): d 8.24 (bs, 1 H, Ar), 7.94 (d, $J$ = 9.0 Hz, 1 H, Ar), 7.80 (d, $J$ = 8.0 Hz, 2 H), 7.49 (t, $J$ = 8.0 Hz, 1 H, Ph), 7.40 (t, $J$ = 8.0 Hz, 2 H, Ph), 7.30-7.28 (m, 3 H, Ar), 7.19-7.18 (m, superimposed, 3 H, Ar, N*H*(CO)), 7.02 (d, $J$ = 9.0 Hz, 1 H, Ar), 5.01 (d, $J$ = 12.5 Hz, 1 H, PhC*H*H), 4.97 (d, $J$ = 12.5 Hz, 1 H, PhCH*H*), 4.18-4.15 (m, superimposed, 3 H, $CHCH_2$, $OCH_2$), 3.86-3.84 (m, 1 H, CHC*H*H), 3.70-3.68 (m, 1 H, CHCH*H*), 3.15-3.13 (bm, 2 H, $OCH_2NH_2$), 2.82 (bm, 2 H, $NH_2$); $^{13}$C NMR (125 MHz, $CDCl_3$): d 169.5, 165.4, 154.4, 139.9, 138.8, 134.4, 133.0, 132.8, 129.0, 138.5, 128.4, 127.0, 126.3, 125.0, 114.1, 71.4, 68.0, 55.4, 42.3, 40.7; FAB-HRMS ($M+Cs^+$) calcd 675.0526, found 675.0546.

**Synthesis of compound 11 as illustrated in Figure 6.** Compound **11** was prepared by the same procedure as for **10** using 40a in lieu of 36b. Yield: (3.31 mg, 13%). $^1$H NMR (500 MHz, methanol-$d^4$): d 8.26 (d, $J$ = 2.0 Hz, 1 H, Ar), 8.04 (dd, $J$ = 2.0, 8.5 Hz, 1 H, Ar), 7.82-7.80 (m, 2 H, Ph), 7.47-7.36 (m, 4 H, 5-ArH, Ph), 4.35 (t, $J$ = 5.0 Hz, 2 H, $OCH_2$), 4.19 (dd, $J$ = 4.0, 14.0 Hz, 1 H, $CHCH_2$), 3.75 (dd, $J$ = 4.0, 14.0 Hz, 1 H, CHC*H*H), 3.68 (t, $J$ = 5.0 Hz, 2 H, $CH_2NH(C=N)$), 3.47 (dd, $J$ = 11.0, 14.0 Hz, 1 H, CHCH*H*).

**Synthesis of compound 12 as illustrated in Figure 6.** To a

solution of the benzyl ester **41a** (0.10 grams, 0.22 mmol) in THF:$H_2O$ (3 mL:1 mL) was added LiOH•$H_2O$ (18.5 mg, 0.44 mmol) at room temperature. After stirring for 4 hours, the reaction mixture was acidified with acetic acid and the solvent removed *in vacuo* to give the crude acid **42a.** To a solution of the acid **42a** in DMF (5 mL) was added *N, N*- diisopropylethylamine (38 mL, 0.22 mmol). After stirring at 50°C for 16 hours, the solvent was removed *in vacuo* to give an oil, which after RP-HPLC (C-18) gave **12** (5.4 mg, 5%) as a yellowish solid. $R_t$ = 14.9 min; $^1$H NMR (600 MHz, $CDCl_3$): d 8.26 (d, *J* =2.0 Hz, 1 H, Ar), 7.67-7.65 (m, 2 H, Ph), 7.64 (dd, *J* = 2.0, 9.0 Hz, Ar), 7.24-7.18 (m, 3 H, Ph), 7.06 (d, *J* = 9.0 Hz, Ar), 4.49 (t, *J* = 4.0 Hz, 2 H, C*H*$_2$OH), 4.15 (dd, *J* = 6.0, 10.0 Hz, 1 H, C*H*CH$_2$), 3.86 (t, *J* = 4.0 Hz, 2 H, C*H*$_2$N(C=NH)NH$_2$), 3.70 (dd, *J* = 6.0, 14.0 Hz, 1 H, CHC*H*H), 3.35 (dd, *J* =10.0, 14.0 Hz, 1 H, CHCH*H*); $^{13}$C NMR (150 MHz, $CDCl_3$): d 167.6, 164.9, 147.2, 141.7, 132.4, 130.5, 129.6, 127.7, 126.8, 125.6, 125.5, 122.2, 112.5, 70.4, 42.6, 28.7, 23.2. Electrospray mass spectrum ($M+H^+$) calcd 495, found 495.

**Synthesis of compounds 39b as illustrated in Figure 6**. To a solution of the azide **38b** (0.031 grams, 0.05 mmol) in THF:$H_2O$ (8 mL:0.04 mL) was added triphenylphosphine (0.026 grams, 0.1 mmol). After stirring at room temperature for 12 hours, the solvent was removed *in vacuo* to give a white solid. The solid was purifed by preparative thin layer chromatography (silica, 20% methanol in dichloromethane) to give **39b** as an oil (0.013 grams, 44%). $R_t$ = 0.1 (silica gel, 10% methanol in dichloromethane); IR (thin film): $n_{max}$ 3361, 3282, 3070, 2922, 2851, 1742, 1650, 1620, 1527, 1456, 1349, 1322, 1280, 1162, 1126, 989, 910 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): d = 8.63 (d, *J* = 10.8 Hz, 1 H, naphthyl), 8.17 (dd, *J* = 1.0, 9.1 Hz, 1 H, naphthyl), 8.02 (d, *J* = 2.5 Hz, 1 H, Ar), 7.92 (d, *J* = 10.3 Hz, 1 H, naphthyl), 7.77 (d, *J* = 10.3 Hz, 1 H, naphthyl), 7.72 (dd, *J* = 2.6, 11.0 Hz, 1 H, Ar), 7.58 (dd, *J* = 8.3, 8.3 Hz, 1 H, naphthyl), 7.49 (dd, *J* = 7.3, 7.3 Hz, 1 H, naphthyl), 7.41 (dd, *J* = 7.5, 7.5 Hz, 1 H, naphthyl), 7.23-7.16 (m, 3 H, Ph),

7.09-7.04 (m, 2 H, Ph), 6.84 (d, *J* = 11.1 Hz, 1 H, Ar), 4.83 (d, *J* = 15.2 Hz, 1 H, C*H*HPh), 4.76 (d, *J* = 15.2 Hz, 1 H, CH*H*Ph), 4.23 (dd, *J* = 5.8, 9.1 Hz, 1 H, C*H*$CH_2$), 4.10-4.04 (bm, 2 H, $OCH_2$), 3.95-3.61 (bm, 5 H, C$H_2$N$H_2$, CHC*H*H), 3.18-3.05 (bm, 1 H, CHC*H*H) ; $^{13}$C NMR (125 MHz, $CDCl_3$): d 169.6, 165.3, 154.2, 146.9, 134.6, 134.5, 134.0, 133.9, 133.2, 129.8, 129.0, 128.6, 128.5, 128.4, 128.2, 127.8, 127.0, 125.9, 124.9, 124.2, 124.1, 114.3, 67.6, 55.9, 42.0, 40.5, 29.6; FAB-HRMS (M+Cs$^+$ calcd 725.0682, found 725.0695.

**Synthesis of compound 13 as illustrated in Figure 6.** Compound **13** was prepared by the same procedure as for **10** using compound 40b in lieu of 36b. Yield: (1.8 mg, 15%) as a yellowish solid. $R_t$ = 21.2 min; $^1$H NMR (500 MHz, methanol-d$^4$): d 8.63 (d, *J* = 9.0 Hz, 1 H, naphthyl), 8.17 (dd, *J* = 1.5, 7.5 Hz, 1 H, naphthyl), 7.94 (d, *J* = 8.5 Hz, 1 H, naphthyl), 7.88 (d, *J* = 2.5 Hz, 1 H, Ar),7.76-7.70 (m, superimposed, 2 H, 6-Ar-H, naphthyl-), 7.57 (ddd, *J* = 1.0, 6.5, 9.3 Hz, 1 H, naphthyl), 7.47 (dd, *J* = 7.5, 8.0 Hz, 1 H, naphthyl), 7.42 (ddd, *J* = 1.0, 7.0, 7.5 Hz, 1 H, naphthyl), 7.25 (d, *J* = 9.0 Hz, 1 H, Ar), 4.36 (t, *J* = 5.0 Hz, 1 H, $CH_2O$), 4.18 (dd, *J* = 4.5, 9.5 Hz, 1 H, C*H*CHH), 3.72 (t, *J* = 5.0 Hz, 2 H, $CH_2NH$), 3.65 (dd, *J* = 4.5, 13.5 Hz, 1 H, CHC*H*H), 3.41 (dd, *J* = 9.5, 13.5 Hz, 1 H, CHCH*H*) ; Electrospray mass spectrum calcd (M+H$^+$) 545, found 545.

**Synthesis of compound 51 as illustrated in Figure 7.** To a solution of aminoethanol (**43**) (1.0 mL, 16.0 mmol) in DMF (30 mL) was added 1,3-Bis-(*tert*-Butoxycarbonyl)-2-methyl-2-thiopseudourea (**48**) (4.81 grams, 16.0 mmol), triethylamine (4.63 mL, 32.0 mmol) and mercury(II) dichloride (4.48 grams, 16.0 mmol) at room temperature. After 4 hours, the reaction mixture was diluted with ethyl acetate and filtered over a short path of celite®. The filtrate was succesively washed with water (2 x 20 mL), brine (20 mL) and dried over $MgSO_4$. After filtration and evaporation of the solvent under reduced pressure the crude compound was purified by flash column

chromatography to give **51** as a colourless solid (4.95 grams, 98%). $R_f$ = 0.43 (silica gel, 50 % ethyl acetate in hexanes); IR (KBr): $n_{max}$ 3329, 3142, 2977, 2934, 2870, 1724, 1644, 1443, 1412, 1360, 1299, 1103, 1052, 1027, 864, 809, 778 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 11.48 (bs, 1 H, $NHCO_2$), 8.66 (m, 1 H, $CH_2NH$), 4.54 (bs, 1 H, OH), 3.74 (t, $J$ = 4.5 Hz, 2 H, $CH_2OH$), 3.54 (dt, $J$ = 5.5, 5.5 Hz, 2 H, $CH_2NH$), 1.47 (s, 9 H, $^t$Bu), 1.45 (s, 9 H, $^t$Bu); $^{13}C$ NMR (125 MHz, $CDCl_3$): d 162.8, 157.4, 153.1, 83.5, 79.2, 63.1, 44.4, 28.2, 28.0; FAB-HRMS ($M+H^+$) calcd 304.1872, found 304.1878.

**Synthesis of compound 52 as illustrated in figure 7.** To a solution of piperazine (**44**) (3.45 mL, 12.0 mmol) in DMF (10 mL) was added 1,3-Bis-(*tert*-Butoxycarbonyl)-2-methyl-2-thiopseudourea (**48**) (0.87 grams, 3.00 mmol) at room temperature. After 14 hours, the reaction mixture was diluted with ethyl acetate and water. The layers were seperated and the organic layer was washed succesively with water (2 x 20 mL), brine (20 mL) and dried over $Na_2SO_4$. The solvent was removed under reduced pressure to give **52** as a colorless solid (0.93 grams, 95%). $R_f$ = 0.34 (silica gel, 10% methanol in dichloromethane); IR (KBr): $n_{max}$ 3294, 2980, 2931, 2856, 1749, 1664, 1605, 1527, 1448, 1367, 1305, 1230, 1149, 1116, 1019, 893, 842, 730, 682 $cm^{-1}$. $^1H$ NMR (500 MHz, methanol-$d^4$): d 3.48 (t, $J$ = 5.0 Hz, 4 H, $(CH_2)_2N(C=N)$, 2.83 (t, $J$ = 5.0 Hz, 4 H, $(CH_2)_2NH$), 1.46 (s, 9 H, $^t$Bu); $^{13}C$ NMR (125 MHz, methanol-$d^4$): d 154.4, 81.4, 48.2, 46.0, 28.6; FAB-HRMS ($M+Na^+$) calcd 341.1226, found 341.1235.

**Synthesis of compound 53 as illustrated in Figure 7.** To a solution of aminoethanethiol (**45**) (114 mg, 1.00 mmol) in DMF (5 mL) was added *N,N'*-Bis-*tert*-Butoxycarbonylthiourea (**49**) (276 mg, 1.00 mmol) and triethylamine (2.79 mL, 2.00 mmol) at room temperature. After 14 hours, the reaction mixture was diluted with 5 mL of $H_2O$ and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. After filtration and evaporation of the

solvent under reduced pressure the crude compound was purified by flash column chromatography (silica gel, 25 % diethyl ether in hexanes) to give **53** as an airsensitive colorless solid (191 mg, 59.8%). $R_f$ = 0.16 (silica, 25 % diethyl ether in hexanes); IR (KBr): $n_{max}$ 3327, 3132, 2978, 2931, 1726, 1643, 1565, 1431, 1363, 1329, 1280, 1227, 1133, 1088, 1058, 855, 809, 760, 606 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 11.45 (bs, 1 H, (C=N)NH(C=O)), 8.61 (bt, $J$ = 5.9 Hz, 1 H, $CH_2NH$), 3.74 (bdt, $J$ = 6.0, 6.5 Hz, 2 H, $CH_2NH$), 2.85 (t, $J$ = 6.5 Hz, 2 H, $CH_2SH$), 1.47 (s, 9 H, $^t$Bu); $^{13}C$ NMR (125 MHz, $CDCl_3$): d 163.4, 156.1, 153.1, 83.2, 79.3, 39.2, 37.0, 28.3, 28.1 ; FAB-HRMS calcd only S-S-dimer observed!

**Synthesis of compound 54 as illustrated in Figure 7**. To a solution of ethylenediamine (**54**) (3.45 mL, 51.6 mmol) in DMF (50 mL) was added 1,3-Bis-(*tert*-Butoxycarbonyl)-2-methyl-2-thiopseudourea (**48**) (3.00 grams, 10.33 mmol), triethylamine (2.88 mL, 20.7 mmol) and mercury(II)chloride (2.81 grams, 10.3 mmol) at room temperature. After 4 hours, the reaction mixture was diluted with 20 mL of ethyl acetate and filtered over a short path of celite®. The filtrate was succesively washed with $H_2O$ (2 x 50 mL), brine (50 mL) and dried over $MgSO_4$. Flash column chromatography (silica gel, 20 % MeOH in ethyl acetate + 2 % v/v $Et_3N$) gave **54** as a colourless solid (1.60 grams, 51.2%). $R_f$ = 0.30 (silica gel, 20 % MeOH in ethyl acetate + 2 % v/v $Et_3N$); IR (KBr): $n_{max}$ 3446, 3389, 3259, 2978, 2819, 1728, 1706, 1656, 1626, 1521, 1485, 1365, 1253, 1171, 1093, 1049, 888, 802, 738, 699, 562 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 11.38 (bs, 1 H, (C=N)NH(C=O)), 8.61 (bt, 1 H, $CH_2NH$(C=N)), 3.45 (bdt, $J$ = 5.5, 5.5 Hz, 2 H, $CH_2NH$), 2.85 (t, $J$ = 5.5 Hz, 2 H, $CH_2NH_2$), 1.46 (s, 9 H, $^t$Bu) ; $^{13}C$ NMR (125 MHz, $CDCl_3$): d 163.4, 156.4, 153.1, 83.1, 79.2, 41.8, 40.9, 28.2; FAB-HRMS ($M+H^+$) calcd 303.2032, found 303.2037.

**Synth sis of compound 55 as illustrated in Figure 7**. To a solution of phenylenediamine (1.08 grams, 0.01 mol) in 5.5 N HCl (10 mL) was added b-alanine (**47**) (1.125g, 0.015 mol) at

room temperature. The reaction mixture was refluxed for 24 hours and then allowed to cool to room temperature. The solvent was removed *in vacuo* to give a precipitate, which was filtered and washed with ether (1.70 grams, 73%). $R_f$ = 0.12 (20% methanol in dichloromethane); $^1$H NMR (500 MHz, $D_2O$): d 7.73-7.72 (m, 2 H, Ar), 7.55-7.53 (m, 2 H, Ar), 3.61-3.55 (m, 4 H, $CH_2CH_2$); $^{13}$C NMR (125 MHZ, $D_2O$): d FAB-HRMS ($M+H^+$) calcd 162.1031, found 162.1029.

**Synthesis of compound 56 as illustrated in Figure 7**. To a solution of ethylenediamine (**46**) (1.0 mL, 0.015 mol) in DMF (10 mL) was added 2-(3,5-Dimethylpyrazolyl)-4,5-dehydroimidazole hydrobromide (**50**) (3.67 grams, 0.015 mol) and *N, N*-diisopropylethylamine (2.61 mL, 0.015 mol) at room temperature. After stirring for 11 hours, ether (12 mL) was added to the reaction mixture and a white precipitate formed. The precipitate was filtered and washed with ether to give **56** (1.59 grams, 51%). IR (KBr): $n_{max}$ 3164, 1681, 1599, 1484, 1287, 1211, 1137, 1069, 952 $cm^{-1}$; $^1$H NMR (500 MHz, $D_2O$): d 3.54 (bs, 4 H, $NHCH_2CH_2NH$), 3.17 (t, $J$ = 6.0 Hz, $CH_2NH$), 2.65 (t, $J$ = 6.0 Hz, $CH_2NH_2$); $^{13}$C NMR (125 MHz, $D_2O$): d 160.9, 45.3, 43.6, 40.3; FAB-HRMS ($M+H^+$) calcd 129.1140, found 129.1134.

**Synthesis of compound 58 as illustrated in Figure 8**. To a solution of 3-nitro-4-fluoro benzoic acid (**30**) (1.59 grams, 8.57 mmol; Aldrich) in benzene (40 mL) was added DMF (0.03 mL, 0.40 mmol) and oxalylchloride (3.73 mL, 20.2 mmol) at 0°C. After 6 hours, the solvent was removed *in vacuo*. The resulting yellow viscous oil (1.73 grams, 8.57 mmol) was dissolved in $CH_2Cl_2$ (20 mL). The solution was cooled to 0°C and triethylamine (1.28 mL, 9.20 mmol) was added. A solution of the protected 2-amino alanine *tert*-butylester **29a** (2.32 grams, 7.70 mmol) in $CH_2Cl_2$ (40 mL) was added. After 4 hours, the reaction mixture was diluted with water and the aqueous phase was extracted with dichloromethane (2 x 50 mL) after phase seperation. The combined organic extracts were washed with saturated aqueous $NaHCO_3$-solution and dried over $MgSO_4$.

After filtration and evaporation of the solvent under reduced pressure the crude compound was purified by flash column chromatography (silica gel, 45 % ethyl acetate in hexanes) to give **58** as a yellow foam (3.90 grams, 98%). $R_f$ = 0.19 (silica gel, 40 % ethyl acetate in hexanes); IR (KBr): $n_{max}$ 3286, 2980, 2936, 1730, 1653, 1619, 1537, 1493, 1448, 1349, 1314, 1159, 1131, 1092 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 8.56 (dd, $^4J$ ($^1H$-$^1H$) = 2.5 Hz, $^4J$ ($^1H$-$^{19}F$) = 7.5 Hz, 1 H, 2-Ar-H), 8.12 (ddd, $^4J$ ($^1H$-$^1H$) = 2.5 Hz, $^4J$ ($^1H$-$^{19}F$) = 4.0 Hz, $^3J$ ($^1H$-$^1H$) = 9.0 Hz, 1 H, 6-Ar-H), 7.84 (d, $J$ = 7.5 Hz, 2 H, *o*-phenyl), 7.58 (d, $J$ =7.5 Hz, 1 H, *p*-phenyl), 7.50 (t, $J$ =7.5 Hz, 2 H, *m*-Ar), 7.34 (dd, $^3J$ ($^1H$-$^1H$) = 9.0 Hz, $^3J$ ($^1H$-$^{19}F$) = 10.0 Hz, Ar-H), 7.13 (t, $J$ = 5.5 Hz, 1 H, (C=O)N*H*), 5.89 (d, $J$ = 8.0 Hz, 1 H, CHN*H*$SO_2$Ph), 3.97-3.92 (m, 2 H, C*H*H, C*H*$CH_2$), 3.60-3.54 (m, 1 H, CH*H*), 1.29 (s, 9 H, $^t$Bu); $^{13}C$ NMR (125 MHz, $CDCl_3$): d 168.1, 164.5, 158.1, 156.0, 138.6, 134.2, 134.1, 133.2, 130.9, 129.2, 127.2, 125.6, 118.9, 118.7, 84.2, 55.8, 42.5, 27.6; FAB-HRMS (M+$Cs^+$) calcd 600.0217, found 600.0195.

**Synthesis of compound 59 as illustrated in Figure 8.**

Compound **59** was prepared by the same procedure as for compound **58** using 2-Naphthalene sulfonyl chloride in lieu of phenyl sulfonyl chloride. Yield: (985 mg, 96%) as an off-white solid. $R_f$ = 0.24 (silica gel, 50 % ethyl acetate in hexanes); IR (KBr): $n_{max}$ 3395, 3297, 3083, 2981, 2937, 1734, 1671, 1620, 1534, 1494, 1460, 1345, 1264, 1156, 1128, 1079, 977, 918, 833, 750, 661, 617, 549, 479 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 8.46 (dd, $^4J$($^1H$-$^1H$) = 2.5 Hz, $^4J$($^1H$-$^{19}F$) = 7.0 Hz, 1 H, 2-Ar-H), 8.38 (d, $J$ = 2.0 Hz, 1 H, naphthyl), 8.02 (ddd, $^4J$($^1H$-$^1H$) = 2.5 Hz, $^4J$($^1H$-$^{19}F$) = 4.0 Hz, $^3J$($^1H$-$^1H$) = 8.8 Hz, 1 H, 6-Ar-H), 7.90 (bd, superimposed, $J$ = 8.5 Hz, 1 H, naphthyl), 7.88 (bd, superimposed, $J$ = 8.5 Hz, 1 H, naphthyl), 7.83 (bd, $J$ = 8.0 Hz, 1 H, naphthyl), 7.79 (dd, $J$ = 2.0, 8.0 Hz, 1 H, naphthyl), 7.62 (ddd, $J$ = 1.0, 7.5, 8.5 Hz, 1 H, naphthyl), 7.58 (ddd, $J$ = 1.0, 7.5, 8.5 Hz, 1 H, naphthyl), 7.27 (br. dd, $J$ = 6.0, 8.5 Hz, 1 H, CONH), 7.18 (bdd, $^3J$($^1H$-$^1H$) = 9.0 Hz, $^3J$($^1H$-$^{19}F$) = 10.0 Hz, 1 H, 5-Ar-H), 6.15 (d, $J$ = 8.0 Hz, 1 H, $NHSO_2$), 4.06 (ddd,

$J$ = 4.0, 5.5, 8.0 Hz, 1 H, C*H*CH$_2$), 3.93 (ddd, $J$ = 4.0, 6.0, 11.0 Hz, 1 H, CHCH*H*), 3.57 (ddd, $J$ = 5.5 Hz, 8.5 Hz, 1 H, CHC*H*H), 1.17 (s, 9 H, $^t$Bu); $^{13}$C NMR (125 MHz, $CDCl_3$): d 168.3, 164.3, 158.0, 155.8, 135.5, 134.7, 134.1, 134.0, 131.8, 130.5, 129.5, 129.1, 128.6, 127.7, 125.4, 122.0, 118.6, 118.4, 83.9, 55.9, 42.3, 27.4; FAB-HRMS (M+Cs$^+$) calcd 650.0373, found 650.0358.

**Synthesis of compound 60 as illustrated in Figure 8**. To a round bottom flask equipped with a magnetic stirring bar was placed NaH (60% suspension in mineral oil) (0.16 grams, 3.96 mmol) and THF (10 mL) at 0°C. To the stirred suspension was added a solution of **51** (0.55 grams, 1.80 mmol) in THF (5 mL). Stirring was continued at this temperature for an additional 30 min and the resulting grey suspension was ready for use. A round bottom flask equipped with a magnetic stirring bar was charged with the aromatic fluoride **58** (0.1 grams, 0.30 mmol) and DMF (10 mL). The solution was cooled to 0°C and 5.5 mL of the previously prepared suspension was added by means of a syringe. After 8 hours at 0°C the reaction was stopped by addition of water (10 mL) and diluted with ethyl acetate. The aqueous phase was seperated and extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were washed successively with $H_2O$ (2 x 10 mL) and brine (10 mL) and dried over $MgSO_4$. After filtration and evaporation under reduced pressure the residue was purified by flash column chromatography (silica, 60% ethyl acetate in hexanes) to give **60** as a yellowish foam (0.15 grams, 66%). $R_f$ = 0.18 (silica gel, 50% ethyl acetate in hexanes); IR (KBr): $n_{max}$ 3331, 2978, 2951, 1733, 1645, 1619, 1532, 1367, 1319, 1277, 1144, 1051, 1025 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): d 11.43 (bs, 1 H, (C=N)NH(C=O)), 8.76 (bt, $J$ = 5.5 Hz, 1 H, $CH_2NH$(C=N)), 8.32 (d, $J$ = 2.5 Hz, 1 H, Ar), 8.00 (dd, $J$ = 2.5, 9.0 Hz, 1 H, Ar), 7.85-7.84 (m, 2 H, Ph), 7.58 (t, $J$ = 8.0 Hz, 1 H, Ph), 7.49 (t, $J$ = 8.0 Hz, 2 H, Ph), 7.20 (d, $J$ = 9.0 Hz, 1 H, Ar), 6.95 (t, $J$ = 8.0 Hz, 1 H, NHCO), 5.84 (d, $J$ = 7.5 Hz, 1 H, $HNSO_2$), 4.28 (t, $J$ = 5.5 Hz, 2 H, $CH_2O$), 3.96-3.87 (m, superimposed, 4

H, CHC$H_2$, C$H_2$NH(C=N)), 3.60-3.54 (m, 1 H, C$H$CH$_2$), 1.50 (s, 9 H, $^t$Bu), 1.48 (s, 9 H, $^t$Bu), 1.28 (s, 9 H, $^t$Bu); $^{13}$C NMR (125 MHz, $CDCl_3$): d 168.2, 165.0, 163.3, 156.5, 154.5, 154.1, 150.9, 139.4, 138.8, 133.1, 132.7, 129.2, 127.2, 126.5, 125.0, 114.5, 84.0, 83.4, 68.1, 55.9, 42.4, 39.4, 28.3, 28.0, 27.6; FAB-HRMS (M+Cs$^+$) calcd 883.1949, found 883.1970.

**Synthesis of compound 11 as illustrated in Figure 8**. To a solution of **60** (30.0 mg, 0.04 mmol) in $CH_2Cl_2$ (2 mL) trifluoroacetic acid (2 mL) was added dropwise. The reaction mixture was stirred at 25°C for 2 hours. The solvents were removed under reduced pressure and the residue was purified by RP-HPLC (C-18) to give **11** as yellowish solid (22.0 mg, 92%). $R_t$ = 12.2 min; IR (KBr): $n_{max}$ 3418, 1679, 1529, 1433, 1354, 1319, 1278, 1198, 1161, 1092, 1046, 932, 837, 802, 756, 688 cm$^{-1}$; $^1$H NMR (500 MHz, methanol-d$^4$): d 8.26 (d, $J$ = 2.0 Hz, 1 H, Ar), 8.04 (dd, $J$ = 2.0, 8.5 Hz, 1 H, Ar), 7.82-7.80 (m, 2 H, Ph), 7.47-7.36 (m, 4 H, Ar), 4.35 (t, $J$ = 5.0 Hz, 2 H, OCH$_2$), 4.19 (dd, $J$ = 4.0, 14.0 Hz, 1 H, C$H$CH$_2$), 3.75 (dd, $J$ = 4.0, 14.0 Hz, 1 H, CHC$H$H), 3.68 (t, $J$ = 5.0 Hz, 2 H, C$H_2$NH(C=N)), 3.47 (dd, $J$ = 11.0, 14.0 Hz, 1 H, CHCH$H$); $^{13}$C NMR (125 MHz, methanol-d$^4$): d 167.7, 155.0, 142.2, 140.7, 134.5, 133.6, 130.0, 128.2, 125.9, 115.7, 69.8, 43.3, 41.8, 25.2; FAB-HRMS (M+H$^+$) calcd 495.1298, found 495.1311.

**Synthesis of compound 61 as illustrated in Figure 8**: To a solution of **58** (100 mg, 0.20 mmol) in DMF (10 mL) was added **53** (68 mg, 0.22 mmol). After stirring at room temperature for 4 hours, the reaction mixture was diluted with water (10 mL) and the aqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed succesively with water (2 x 10 mL) and brine (20 mL) and dried over $Na_2SO_4$. After filtration and evaporation under reduced pressure the residue was purified by flash column chromatography (silica gel, 50 % ethyl acetate in hexanes) to give **61** as a yellowish foam (110 mg, 73%). $R_f$ = 0.48 (silica gel, 60% ethyl acetate in hexanes); IR (film): $n_{max}$ 3318, 2925,

1723, 1623, 1517, 1412, 1324, 1158 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 11.47 (bs, 1 H, (C=N)NH(C=O)), 8.59 (d, *J* = 2.5 Hz, 1 H, Ar), 8.56 (t, *J* = 10.0 Hz, 1 H, NH), 8.43 (t, *J* = 10.0 Hz, 1 H, NH), 7.93 (dd, *J* = 2.5 Hz, 10.0 Hz, 1 H, Ar), 7.84 (d, *J* = 9.0 Hz, 2 H, Ph), 7.53 (t, *J* = 10.0 Hz, 1 H, Ph), 7.46 (t, *J* = 10.0 Hz, 2 H, Ph), 7.21 (d, *J* = 10.0 Hz, 1 H, Ar), 6.81 (t, *J* = 10.0 Hz, 1 H, CONH), 5.87 (d, *J* = 10.0 Hz, 1 H, $NHSO_2$), 3.98-3.93 (m, 1 H, $CHCH_2$), 3.87-3.82 (m, 1 H, CHC*H*H), 3.72-3.55 (m, 5 H, CHCH*H*, $NHCH_2$, $CH_2NH(C=N)$), 1.52 (s, 9 H, $^t$Bu), 1.47 (s, 9 H, $^t$Bu), 1.27 (s, 9 H, $^t$Bu); $^{13}C$ NMR (125 MHz, $CDCl_3$): d 168.4, 165.7, 163.3, 156.6, 153.2, 146.9, 139.1, 134.7, 133.0, 131.4, 129.1, 127.2, 126.2, 121.0, 114.4, 83.7, 83.5, 79.5, 56.2, 42.4, 42.2, 39.0, 28.3, 28.0, 27.6; FAB-HRMS ($M+Cs^+$) calcd 882.2109, found 882.2129.

Synthesis of compound **14 as illustrated in Figure 8**. Compound **14** was prepared by the same procedure as **11** using **61** in lieu of **60**. Yield: (33.2 mg,92%) as a yellow solid. $R_t$ = 15.9 min; IR (KBr): $n_{max}$ 3364, 3245, 2998, 2584, 1669, 1624, 1555, 1520, 1433, 1313, 1198, 1161, 923, 756, 722 $cm^{-1}$; $^1H$ NMR (500 MHz, methanol-$d^4$): d 8.61 (d, *J* = 2.5 Hz, 1 H, Ar), 7.92 (dd, *J* = 2.5, 9.0 Hz, 1 H, Ar), 7.81 (d, *J* = 7.0 Hz, 2 H, Ph), 7.47-7.40 (m, 3 H, Ph), 7.11 ( d, *J* = 9.0 Hz, 1 H, Ar), 4.19 (dd, *J* = 5.0, 9.0 Hz, 1 H, C*H*$CH_2$), 3.72 (dd, *J* = 5.0, 13.5 Hz, 1 H, CHC*H*H), 3.67 (t, *J* = 6.0 Hz, 2 H, $NHCH_2$), 3.52 (t, *J* = 6.0 Hz, 2 H, $NHCH_2$), 3.46 (dd, *J* = 9.0, 13.5 Hz, 1 H, CHCH*H*); $^{13}C$ NMR (125 MHz, methanol-$d^4$): d 168.3, 159.0, 148.0, 142.1, 135.8, 133.6, 132.9, 130.0, 127.8, 125.0, 122.3, 114.8 43.2, 42.5, 41.1, 31.1; FAB-HRMS ($M+H^+$) calcd 494.1458, found 494.1444.

**Synthesis of compound 62 as illustrated in Figure 8**. To a solution of **54** (1.60 mg, 5.0 mmol) in THF (50 mL) was added NaH (60 % suspension in mineral oil) (200 mg, 5.00 mmol) at 0°C. After 15 min the resulting thiolate solution was ready for use. To a solution of **58** (100 mg, 0.20 mmol) in DMF (10 mL) was added the thiolate solution (5.0 mL, 0.5 mmol) by

syringe. After 12 hours at room temperature the reaction was stopped by addition of water (10 mL) and diluted with ethyl acetate. After phase seperation the aqueous phase was extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were washed succesively with water (2 x 10 mL) and brine (10 mL) and dried over $MgSO_4$. After filtration and evaporation under reduced pressure the residue was purified by flash column chromatography (silica gel, 40 % ethyl acetate in hexanes) to give **62** as a yellowish foam (35 mg, 23%). $R_f$ = 0.32 (silica gel, 40 % ethyl acetate in hexanes); $^1$H NMR (500 MHz, $CDCl_3$): d 11.45 (bs, 1 H, (C=N)NH(C=O)), 8.65 (bt, superimposed, $J$ = 4.5 Hz, 1 H, $CH_2NH$(C=N)), 8.63 (d, superimposed, $J$ = 2.0 Hz, 1 H, Ar), 8.22 (d, $J$ = 8.5 Hz, 1 H, Ar), 8.15 (dd, $J$ = 2.0, 8.5 Hz, 2 H, Ar), 7.84 (d, $J$ = 8.0 Hz, 2 H, Ph), 7.56 (t, $J$ = 7.5 Hz, 1 H, Ph), 7.48 (bdd, $J$ = 7.0, 8.0 Hz, 2 H, Ph), 6.98 (t, $J$ = 5.5 Hz, 1H, CONH), 5.72 (d, $J$ = 7.0 Hz, 1 H, $NHSO_2$), 3.99-3.93 (bm, 1 H, $CHCH_2$), 3.88 (ddd, $J$ = 4.5, 5.5, 13.5 Hz, 1 H, CHC*H*H), 3.70-3.58 (m, 3 H, CHCH*H*, C*H*$_2$NH(C=N)), 3.26 (t, $J$ = 8.0 Hz, 2 H, $SCH_2$), 1.57 (s, 9 H, $^t$Bu), 1.50 (s, 9 H, $^t$Bu), 1.30 (s, 9 H, $^t$Bu); $^{13}$C NMR (125 MHz, $CDCl_3$): d 168.2, 165.1, 163.4, 156.3, 153.1, 145.3, 141.0, 138.9, 133.1, 132.3, 130.3, 129.2, 127.7, 127.2, 124.7, 84.0, 83.5, 79.6, 55.9, 42.4, 39.2, 30.1, 28.4, 28.0, 27.6; FAB-HRMS ($M+Cs^+$) calcd 899.1720, found 899.1753.

**Synthesis of compound 15 as illustrated in Figure 8.**

Compound **15** was prepared by the same procedure as for **11** using **62** in lieu of **60**. Yield: (23.0 mg, 92%) as a yellow solid. $R_t$ = 16.0 min; $^1$H NMR (500 MHz, methanol-d$^4$): d 8.58 (d, $J$ = 2.0 Hz, 1 H, Ar), 8.06 (dd, $J$ = 2.0, 8.5 Hz, 1 H, Ar), 7.82 (d, $J$ = 7.0 Hz, 2 H, Ph), 7.71 (d, $J$ = 8.5 Hz, 1 H, Ph), 7.48-7.41 (m, 3 H, Ar), 4.23 (dd, $J$ = 5.0, 9.0 Hz, 1 H, C*H*$CH_2$), 3.80-3.76 (m, 1 H, CHC*H*H), 3.56 (t, $J$ = 6.5 Hz, 2 H, C*H*$_2$NH(C=N)), 3.50-3.43 (m, 1 H, CHCH*H*), 3.34 (t, $J$ = 6.5 Hz, 2 H, $SCH_2$); $^{13}$C NMR (125 MHz, methanol-d$^4$): d 167.6, 155.2, 142.1, 140.7, 133.5, 133.3, 132.5, 128.3, 128.0, 126.0, 43.4, 40.7, 32.3; FAB-HRMS($M+H^+$) calcd 511.1070, found 511.1058.

**Synthesis of compound 65 as illustrated in Figure 8**. To a solution of **58** (100 mg, 0.20 mmol) in DMF (10 mL) was added **52** (68 mg, 0.22 mmol). After 6 hours, the reaction mixture was diluted with water (25 mL) and ethyl acetate. After phase separation the aqueous phase was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed succesively with water (2 x 20 mL) and brine (20 mL) and dried over $Na_2SO_4$. After filtration and evaporation under reduced pressure the residue was purified by flash column chromatography (silica gel, 40 Æ 50 % ethyl acetate in hexanes) to give **65** as a yellowish foam (120 mg, 83%). $R_f$ = 0.30 (silica gel, 40 % ethyl acetate in hexanes); IR (film): $n_{max}$ 3266, 2977, 1743, 1621, 1520, 1451, 1367, 1304, 1158, 1130, 1094, 1014 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 10.22 (bs, 1 H, (C=N)*H*N(C=O)), 8.29 (d, *J* = 2.5 Hz, 1 H, Ar), 7.92 (dd, *J* = 2.5, 9.0 Hz, 1 H, Ar), 7.85-7.84 (m, 2 H, Ph), 7.83-7.82 (m, 1 H), 7.56 (t, *J* = 7.0 Hz, 1 H, Ph), 7.48 (t, *J* = 7.0 Hz, 2 H, Ar-H), 7.08 (d, *J* = 9.0 Hz, 1 H, Ar-*H*), 6.93 (t, *J* = 6.0 Hz, 1 H, CO(N*H*)), 5.85 (d, *J* = 8.0 Hz, 1 H, N*H*SO2), 3.96-3.87 (m, 2 H, C*H*$CH_2$, CHC*H*H), 3.80-3.70 (bm, 4 H, NH(C*H*$_2$)$_2$), 3.59-3.54 (m, 1 H, CHCH*H*), 3.23-3.21 (m, 4 H, N($CH_2$)$_2$), 1.48 (s, 18 H, $^t$Bu), 1.26 (s, 9 H, $^t$Bu); $^{13}C$ NMR (500 MHz, $CDCl_3$): d 168.3, 165.3, 155.2, 147.5 140.9, 138.8, 133.1, 132.0, 129.2, 127.2, 126.3, 126.0, 119.9, 84.0, 56.0, 50.3, 42.2, 28.1, 27.6; FAB-HRMS ($M+Cs^+$) calcd 908.2265, found 908.2233.

**Synthesis of compound 16 as illustrated in Figure 8**. Compound **16** was prepared by the same procedure as for **11** using 66 in lieu of 65. Yield: (15.0 mg, 93%) as a yellowish solid. $R_t$ = 15.3 min; IR (KBr): $n_{max}$ 3367, 3239, 2925, 2857, 1662, 1613, 1523, 1449, 1388, 1320, 1199, 1173, 1135, 1093, 992, 837, 802, 721 $cm^{-1}$; $^1H$ NMR (500 MHz, methanol-$d^4$): d 8.22 (d, *J* = 2.0 Hz, 1 H, Ar), 7.95 (dd, *J* = 2.0, 8.5 Hz, 1 H, Ar), 7.79 (m, 2 H, Ph), 7.47-7.38 (m, 3 H, Ph), 7.32 (d, *J* = 8.5 Hz, 1 H, Ar), 4.21 (dd, *J* = 5.0, 9.0 Hz, 1 H, C*H*$CH_2$), 3.74 (dd, *J* = 5.0, 10.0 Hz, 1 H, CHC*H*H), 3.67-3.65 (m, 4 H, N($CH_2$)$_2$), 3.49-3.44 (m, 1 H, CHCH*H*), 3.31-3.29 (m, 4 H, N($CH_2$)$_2$); $^{13}C$ NMR (125 MHz,

methanol-$d^4$): d 172.6, 167.9, 158.4, 148.3, 142.8, 142.2, 129.9, 56.6, 50.9, 46.3, 43.3; FAB-HRMS ($M+H^+$) calcd 520.1614, found 520.1630.

**Synthesis of compound 63 as illustrated in Figure 8**. To a solution of **51** (130 mg, 0.43 mmol) in THF (5.0 mL) was added NaH (60 % suspension in mineral oil) (70 mg, 1.74 mmol) at 0°C. Stirring was continued at this temperature for additional 15 min and the resulting grey suspension was ready for use. To a solution of **59** (200 mg, 0.39 mmol) in DMF (20 mL) was added the alkoxide (2.5 mL). After stirring for 1 hour at 0°C the remaining 2.5 mL of the alkoxide was added. After 3 hours at 0°C the reaction was stopped by addition of 10 mL of a saturated aqueous $NH_4Cl$-solution and diluted with ethyl acetate. After phase seperation the aqueous phase was extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were washed succesively with $H_2O$ (2 x 10 mL) and brine (10 mL) and dried over $MgSO_4$. After filtration and evaporation under reduced pressure the residue was purified by flash column chromatography (silica gel, 50 % ethyl acetate in hexanes) to give **63** as a yellow solid (211 mg, 69%). $R_f$ = 0.16 (silica gel, 50 % ethyl acetate in hexanes); IR (KBr): $n_{max}$ 3330, 2979, 2934, 1728, 1620, 1570, 1531, 1416, 1329, 1281, 1156, 1079, 1023, 970, 916, 816, 753, 660, 618, 552, 477 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 11.45 (bs, 1 H, (C=N)NH(C=O)), 8.78 (bt, 1 H, $CH_2NH$(C=N)), 8.37 (s, 1 H, Ar), 8.26 (d, $J$ = 2.0 Hz, 1 H, naphthyl), 7.92-7.87 (2 x d, $J$ = 8.0 Hz, 2 H, naphthyl), 7.90 (d, $J$ = 8.5 Hz, 1 H, Ar), 7.83 (d, $J$ = 8.5 Hz, 1 H, naphthyl), 7.79 (dd, $J$ = 2.0, 8.5 Hz, 1 H, naphthyl), 7.64-7.55 (2 x br. dd, 2 H, naphthyl), 7.07 (d, $J$ = 8.5 Hz, 1 H, Ar), 6.90 (dd, $J$ = 5.5, 5.5 Hz, 1 H, $CH_2NH$(C=O)), 5.95 (d, $J$ = 7.5 Hz, 1 H, $NHSO_2$), 4.22 (t, $J$ = 5.3 Hz, 2 H, $OCH_2$), 4.02 (ddd, $J$ = 4.0, 7.5, 8.5 Hz, 1 H, $CHCH_2$), 3.93-3.83 (m, superimposed, 3 H, $CHCHH$, $CH_2NH$(C=N)), 3.55 (ddd, $J$ = 5.5, 8.5, 13.5 Hz, 1 H, $CHCHH$), 1.50 (s, 9 H, $^t$Bu), 1.47 (s, 9 H, $^t$Bu), 1.17 (s, 9 H, $^t$Bu); $^{13}C$ NMR (125 MHz, $CDCl_3$): d 168.3, 164.9, 156.4, 154.0, 152.9, 139.3, 135.6, 134.9, 132.6, 132.0,

129.6, 129.2, 129.1, 128.7, 127.8, 127.7, 127.6, 126.3, 125.0, 122.1, 114.4, 84.0, 83.5, 68.0, 56.1, 42.3, 39.5, 28.3, 28.0, 27.5; FAB-HRMS ($M+Cs^+$) calcd 933.2105, found 933.2116.

**Synthesis of compound 17 as illustrated in Figure 8.** Compound **17** was prepared by the same procedure as for **11** using 63 in lieu of 60. Yield: (32.7 mg, 99%) as an off white to brownish solid. $R_t$ = 14.5 min. IR (KBr): $n_{max}$ = 3421, 2999, 2898, 1657, 1635, 1528, 1383, 1351, 1322, 1276, 1198, 1157, 1132, 1080, 1046, 979, 823, 754, 660, 550 $cm^{-1}$; $^1H$ NMR (500 MHz, methanol-$d^4$): d 8.15 (s, 1 H, naphthyl), 7.93 (d, $J$ = 2.0 Hz, 1 H, Ar), 7.72 (d, $J$ = 8.0 Hz, 1 H, naphthyl), 7.69-7.58 (m, 4 H, naphthyl, Ar), 7.42-7.35 (2 x ddd, superimposed, 2 H, naphthyl), 6.92 (d, $J$ = 9.0 Hz, 1 H, Ar), 4.21 (dd, $J$ = 4.5, 9.8 Hz, 1 H, C*H*$CH_2$), 4.13 (t, $J$ = 5.0 Hz, 2 H, $OCH_2$), 3.61 (dd, $J$ = 4.5, 13.5 Hz, 1 H, CHC*H*H), 3.57 (t, $J$ = 4.5 Hz, 2 H, $CH_2$NH(C=N)), 3.28 (dd, $J$ = 9.8 Hz, 13.5 Hz, 1 H, CHCH*H*); $^{13}C$ NMR (125 MHz, methanol-$d^4$): d 172.8, 167.1, 159.3, 154.9, 140.1, 139.5, 135.9, 134.1, 133.4, 130.3, 130.2, 129.5, 128.8, 128.7, 128.4, 127.3, 125.7, 123.5, 115.3, 69.7, 56.8, 43.1, 41.8; FAB-HRMS ($M+H^+$) calcd 545.1455, found 545.1471.

**Synthesis of compound 64 as illustrated in Figure 8.** To a solution of **59** (50 mg, 0.10 mmol) in 1-methyl-2-pyrrolidinone (1 mL) was added **53** (58 mg, 0.19 mmol) at room temperature. After 4 hours, the reaction mixture was diluted with water (10 mL) and the aqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed succesively with water (2 x 5 mL) and brine (5 mL) and dried over $MgSO_4$. After filtration and evaporation under reduced pressure the residue was purified by flash column chromatography (silica gel, 50 % ethyl acetate in hexanes) to give **64** as a yellow solid (76 mg, 99%). $R_f$ = 0.22 (silica gel, 50 % ethyl acetate in hexanes); IR (KBr): $n_{max}$ 3300, 3065, 2975, 2931, 1734, 1660, 1620, 1535, 1497, 1347, 1261, 1159, 1129, 1079, 972, 917, 817, 751, 661, 551, 477 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 11.49 (bs, 1 H, (C=N)NH(C=O)), 8.58 (bt, 1H, $CH_2NH$(C=N)), 8.47 (d, $J$ =

2.0 Hz, 1 H, Ar), 8.41 (dd, $J$ = 5.5 Hz, 1 H, N*H*$CH_2$), 8.37 (d, $J$ = 2.0 Hz, 1 H, naphthyl), 7.90-7.84 (m, superimposed, 3 H, naphthyl), 7.86 (dd, $J$ = 2.0, 9.0 Hz, 1 H, Ar), 7.79 (dd, $J$ = 2.0, 8.5 Hz, 1 H, naphthyl), 7.59 (ddd, $J$ = 1.5 Hz, 7.0, 7.0 Hz, 1 H, naphthyl), 7.54 (ddd, $J$ = 1.5 Hz, 7.0, 7.0 Hz, 1 H, naphthyl), 7.12 (d, $J$ = 9.0 Hz, 1 H, Ar), 6.69 (t, $J$ = 5.5 Hz, 1 H, $CH_2$N*H*(C=O)), 5.89 (d, $J$ = 8.0 Hz, 1 H, $NHSO_2$), 4.03 (ddd, $J$ = 4.0, 8.0, 8.5 Hz, 1 H, C*H*$CH_2$), 3.85 (ddd, $J$ = 4.0, 6.0, 14.0 Hz, 1 H, CHC*H*H), 3.70 (bdt, $J$ = 5.5, 5.5 Hz, 2 H, NHC$H_2$), 3.61-3.50 (m, 3 H, CHCH*H*, C$H_2$NH(C=N)), 1.52 (s, 9 H, $^t$Bu), 1.47 (s, 9 H, $^t$Bu), 1.18 (s, 9 H, $^t$Bu); $^{13}$C NMR (125 MHz, $CDCl_3$): d 168.5, 165.6, 156.6, 153.2, 146.9, 136.0, 134.8, 134.6, 132.0, 131.3, 129.6, 129.2, 128.9, 128.6, 127.8, 127.6, 126.0, 122.2, 120.8, 114.3, 83.8, 83.6, 56.4, 42.4, 42.2, 39.1, 28.3, 28.0, 27.6; FAB-HRMS (M+Cs$^+$) calcd 932.2265, found 932.2285.

**Synthesis of compound 18 as illustrated in Figure 8.**

Compound **18** was prepared by the same procedure as **11** using 64 in lieu of 60. Yield: (81.7 mg, 90%) as an orange yellow solid. $R_t$ = 12.4 min; IR (KBr): $n_{max}$ 3364, 1676, 1624, 1556, 1520, 1426, 1315, 1241, 1200, 1158, 1133, 1076, 1025, 999, 824, 757, 719, 660, 549, 479 cm$^{-1}$; $^1$H NMR (500 MHz, methanol-$d^4$): d 8.17 (bs, 1 H, naphthyl), 8.14 (d, $J$ = 2.0 Hz, 1 H, Ar), 7.72 (d, $J$ = 8.0 Hz, 1 H, naphthyl), 7.68-7.65 (m, 2 H, naphthyl), 7.57 (bd, superimposed, $J$ = 9.5 Hz, 1 H, naphthyl), 7.55 (dd, superimposed, $J$ = 2.0, 9.0 Hz, 1 H, Ar), 7.41 (ddd, $J$ = 1.5, 7.0, 8.0 Hz, 1 H, naphthyl), 7.36 (ddd, $J$ = 1.5, 7.0, 8.0 Hz, 1 H, naphthyl), 6.74 (d, $J$ = 9.0 Hz, 1 H, Ar), 4.25 (dd, $J$ = 4.5, 10.0 Hz, 1 H, C*H*$CH_2$), 3.62 (dd, $J$ = 4.5, 14.0 Hz, 1 H, CHC*H*H), 3.52 (t, $J$ = 6.0 Hz, 2 H, NHC$H_2$), 3.41 (t, $J$ = 6.0 Hz, 2 H, NHC$H_2$), 3.30 (dd, $J$ = 10.0, 14.0 Hz, 1 H, CHCH*H*); $^{13}$C NMR (125 MHz, methanol-$d^4$): d 173.0, 167.8, 147.8, 139.5, 135.9, 135.3, 133.4, 130.3, 130.2, 129.3, 128.7, 128.6, 128.3, 127.2, 123.5, 121.5, 114.5, 57.0, 42.9, 42.5, 41.5; FAB-HRMS (M+Na$^+$) calcd 566.1434, found 566.1453.

**Synthesis of compound 66 as illustrated in Figure 8**. To a solution of **59** (150 mg, 0.29 mmol) in DMF (5 mL) was added **52** (190 mg, 0.58 mmol) at room temperature. After 20 hours, the reaction mixture was diluted with water (25 mL) and ethyl acetate. After phase seperation, the aqueous phase extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed succesively with water (2 x 20 mL) and brine (20 mL) and dried over $MgSO_4$. After filtration and evaporation under reduced pressure the residue was purified by flash column chromatography (silica gel, 40 % ethyl acetate in hexanes) to give **66** as a yellow solid (240 mg, 99%). $R_f$ = 0.33 (silica gel, 50 % ethyl acetate in hexanes); IR (KBr): $n_{max}$ 3397, 2979, 2933, 1741, 1610, 1524, 1454, 1367, 1303, 1239, 1157, 1015, 975, 834, 752, 661, 615, 552, 477 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 11.49 (bs, 1H, (C=N)NH(C=O), 8.38 (bs, 1 H, naphthyl), 8.24 (d, $J$ = 2.0 Hz, 1 H, Ar), 7.90 (bd, $J$ = 7.5 Hz, 1 H, naphthyl), 7.87 (brd, $J$ = 9.0 Hz, 1 H, naphthyl), 7.83 (dd, superimposed, $J$ = 2.0, 8.5 Hz, 1 H, Ar), 7.82 (d, superimposed, $J$ = 8.0 Hz, 1 H, naphthyl), 7.79 (dd, $J$ = 2.0, 8.5 Hz, 1 H, naphthyl), 7.64-7.55 (2 x bddd, superimposed, 2 H, naphthyl), 7.13 (bm, 1 H, NH(C=O)), 6.98 (d, $J$ = 9.0 Hz, 1 H, Ar), 4.01 (ddd, $J$ = 3.5, 8.0, 9.0 Hz, 1 H, C*H*$CH_2$), 3.88 (ddd, $J$ = 4.0, 6.0, 13.5 Hz, 1 H, CHC*H*H), 3.73 (bm, 4 H, $NCH_2$), 3.55 (ddd, $J$ = 5.5, 8.5, 13.5 Hz, 1 H CHCH*H*), 3.18 (bm, 4 H, $NCH_2$), 1.48 (s, 18 H, $^t$Bu), 1.15 (s, 9 H, $^t$Bu); $^{13}C$ NMR (125 MHz, $CDCl_3$): d 168.6, 165.1, 155.2, 147.3, 140.9, 135.6, 134.9, 132.0, 129.6, 129.2, 129.0, 128.7, 127.8, 127.7, 126.2, 126.0, 122.1, 119.8, 119.7, 83.9, 56.1, 50.3, 42.2, 28.2, 28.0, 27.3; FAB-HRMS ($M+Cs^+$) calcd 958.2422, found 958.2458.

**Synthesis of compound 19 as illustrated in Figure 8**. Compound **19** was prepared by the same procedure as for **11** using 66 in lieu of 60. Yield: (31.9 mg, 93%) as a yellowish solid. $R_t$ = 11.1 min; IR (KBr): $n_{max}$ 3401, 3297, 3251, 2996, 2928, 1659, 1613, 1523, 1451, 1385, 1323, 1199, 1157, 1138, 1078, 992, 808, 753, 720, 660, 549 $cm^{-1}$; $^1H$ NMR (500 MHz, methanol-$d^4$): d 8.19 (bs, 1 H, naphthyl), 7.93 (d, $J$ = 2.0 Hz, 1 H,

Ar), 7.76 (bd, $J$ = 9.0 Hz, 1 H, naphthyl), 7.71-7.61 (m, superimposed, 3 H, naphthyl, Ar), 7.55 (dd, $J$ = 2.0 Hz, 8.8 Hz, 1 H, naphthyl), 7.44-7.36 (2 x ddd, superimposed, 2 H, naphthyl), 6.91 (d, $J$ = 8.5 Hz, 1 H, Ar), 4.21 (dd, $J$ = 4.5, 9.5 Hz, 1 H, C*H*$CH_2$), 3.61 (dd, $J$ = 4.5, 13.5 Hz, 1 H, CHC*H*H), 3.55 (m, 4 H, $NCH_2$), 3.29 (dd, $J$ = 9.5, 13.5 Hz, 1 H, CHCH*H*), 3.15-3.09 (m, 4 H, $NCH_2$); $^{13}C$ NMR (125 MHz, methanol-$d^4$): d 167.6, 158.5, 148.2, 142.1, 139.4, 136.0, 133.5, 133.3, 130.4, 130.3, 129.7, 128.9, 128.5, 127.3, 126.7, 123.6, 121.2, 50.9, 49.6, 48.6, 46.4; FAB-HRMS (M+$Cs^+$) calcd 702.0747, found 702.0784.

**Synthesis of compound 67 as illustrated in Figure 9.** To a solution of **57** (0.10 grams, 0.20 mmol) in DMF (8 mL) was added **55** (0.038 grams, 0.22 mmol) and triethylamine (0.06 mL, 0.44 mmol) at room temperature. After stirring at 25°C for 16 hours, the reaction mixture was diluted with EtOAc (10 mL) and water (10 mL). The layers were seperated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic extracts were collected and washed with water (2 x 10 mL) and brine (20 mL) and dried over $Na_2SO_4$. After filtration and evaporation under reduced pressure the residue was purified by flash chromatography (silica, ethyl acetate) to give **67** as a yellowish solid (110 mg, 92%). $R_f$ = 0.43 (silica, ethyl acetate); $^1H$ NMR (500 MHz, methanol-$d^4$): d 8.57 (d, $J$ = 2.0 Hz, 1 H, Ar), 7.96 (bm, 1 H, Ar), 7.83 (dd, $J$ = 2.0, 9.0 Hz, 1 H, Ar), 7.80-7.78 (m, 2 H, Ar), 7.48-7.39 (m, 4 H, Ar), 7.18 (dd, $J$ = 4.0, 6.0 Hz, 2 H), 7.06 (d, $J$ = 9.0 Hz, 1 H, Ar), 4.12 (dd, $J$ = 6.0, 8.0 Hz, 1 H, $CH_2CH$), 3.89 (t, $J$ =7.0 Hz, 2 H, $CH_2$Ar), 3.65 (dd, $J$ = 6.0, 14.0 Hz, 1 H, C*H*HCH), 3.46 (dd, $J$ = 8.0, 14.0 Hz, 1 H, CH*H*CH), 3.26 (t, $J$ = 7.0 Hz, 2 H, $CH_2$NH), 1.22 (s, 9 H, $^t$Bu); $^{13}C$ NMR (125 MHz, methanol-$d^4$): d 170.4, 168.1, 164.8, 153.6, 147.9, 142.2, 135.6, 133.6, 132.6, 132.4, 130.1, 128.1, 127.7, 123.5, 121.8, 114.9, 83.3, 57.3, 43.2, 42.3, 27.9; Electrospray mass spectrum (M+$H^+$) calcd 609, observed 609.

**Synthesis of compound 20 as illustrated in Figure 9**. To a solution of **57** (0.068 grams, 0.11 mmol) in $CH_2Cl_2$ (2 mL) was added trifluoroacetic acid (2 mL) at room temperature. After 4 hours, the solvent was removed *in vacuo* to give an oil which after RP-HPLC (C-18) gave **20** as a yellow solid (0.056, 97%). $^1$H NMR (500 MHz, methanol-d$^4$): d 8.65 (d, *J* = 1.0 Hz, 1 H, Ar), 7.93 (dd, *J* = 1.0, 9.0 Hz, 1 H, Ar), 7.81 (d, *J* = 8.0 Hz, 2 H, Ph), 7.74 (dd, *J* = 3.0, 6.0 Hz, 2 H, Ar), 7.58 (dd, *J* = 3.0, 6.0 Hz, Ar), 7.48 (t, *J* = 7.0 Hz, 1 H, Ph), 7.43 (t, *J* = 8.0 Hz, 2 H, Ph), 7.16 (d, *J* = 9.0 Hz, 1 H, Ar), 4.20 (dd, *J* = 5.0, 9.0 Hz, 1 H, C*H*CHH), 4.04 (t, *J* = 6.5 Hz, 2 H, C*H*$_2$Ar), 3.74 (dd, *J* = 5.0, 14.0 Hz, 1 H, CHC*H*H), 3.54 (t, *J* = 6.5 Hz, 2 H, $CH_2$NH), 3.45 (dd, *J* = 9.0, 14.0 Hz, 1 H, CHCH*H*); $^{13}$C NMR (125 MHz, methanol-d$^4$): d 172.6, 168.1, 152.6, 147.3, 142.0, 135.7, 133.5, 133.1, 132.4, 132.3, 130.0, 127.9, 127.8, 127.4, 122.5, 114.8, 114.6, 56.8, 43.2, 41.2, 27.2; FAB-HRMS (M+Cs$^+$) calcd 685.0482, found 685.0461.

**Synthesis of compound 68 as illustrated in Figure 9**. To a solution of **57** (0.06 grams, 0.13 mmol) in DMF (10 mL) was added **56** (0.03 grams, 0.14 mmol) and triethylamine (0.04 mL, 0.29 mmol) at room temperature. After 12 hours, the solvent was removed *in vacuo* to give **68** as a crude yellow oil (0.09 grams, 110%). $R_f$ = 0.23 (40% methanol in dichloromethane); $^1$H NMR (500 MHz, methanol-d$^4$): d 8.63 (d, *J* = 2.0 Hz, 1 H, Ar), 7.93 (dd, *J* = 2.0, 9.0 Hz, 1 H, Ar), 7.82 (d, *J* = 6.5 Hz, 2 H, Ph), 7.48-7.42 (m, 3 H, Ph), 7.09 (d, *J* = 9.0 Hz, 1 H, Ar), 4.08-4.06 (m, 1 H, C*H*CHH), 3.68-3.62 (m, superimposed, 5 H, $NHCH_2CH_2NH$, CHC*H*H), 3.50-3.44 (m, 1 H, CHCH*H*), 3.30 (t, *J* = 3.5 Hz, 2 H, C*H*$_2$NHAr), 1.24 (s, 9 H, $^t$Bu); Electrospray mass spectrum calcd (M+H$^+$) 573, found 573.

**Synthesis of compound 21 as illustrated in Figure 9**. To a solution of **68** (0.09 grams, 0.14 mmol) in $CH_2Cl_2$ (5 mL) was added trifluoroacetic acid (5 mL) at room temperature. After 4 hours, the solvent was removed *in vacuo* to give an oil which after RP-HPLC (C-18) gave **21** as a yellow solid (0.07 grams,

83%) $R_t$ = 14.0 min; $^1$H NMR (500 MHz, methanol-d$^4$): d 8.64 (bs, 1 H, Ar), 7.94 (d, *J* = 9.0 Hz, 1 H, Ar), 7.82 (d, *J* = 7.0 Hz, 2 H, Ph), 7.48 (t, *J* = 7.0 Hz, 1 H, Ph), 7.43 (t, *J* = 7.0 Hz, 1 H, Ph), 7.12 (d, *J* = 9.0 Hz, 1 H, Ar), 4.20 (dd, *J* = 5.0, 9.0 Hz, 1 H, C*H*CH$_2$), 3.73 (dd, *J* = 5.0, 14.0 Hz, 1 H, CHC*H*H), 3.70-3.66 (m, superimposed, 7 H, NCH$_2$CH$_2$N, CH$_2$N(C=N)), 3.52 (t, *J* = 6.0 Hz, 2 H, CH$_2$NHAr), 3.45 (dd, *J* = 9.0, 14.0 Hz, 1 H, CHCH*H*); $^{13}$C NMR (125 MHz, methanol-d$^4$): d 172.7, 168.3, 161.6, 148.0, 142.1, 135.8, 133.5, 132.9, 130.0, 128.0, 127.7, 122.3, 114.9, 56.7, 44.1, 43.2, 42.9, 42.7; FAB-HRMS (M+H$^+$) calcd 520.1614, found 520.1630.

**Synthesis of compound 69 as illustrated in Figure 10.** To a solution of the fluoride **57** (0.10 grams, 0.20 mmol) in dry DMF (10 mL) at room temperature a stream of $NH_{3(g)}$ was bubbled through for 1 hour. After stirring for 4 hours, the reaction mixture was diluted with ethyl acetate and water. The layers were seperated and the organic layer was washed with water (2 x 10 mL), brine (20 mL) and dried ($Na_2SO_4$). The solvent was removed *in vacuo* to give **61** as a yellowish oil (0.09 grams, 93%). $R_f$ = 0.25 (silica, 50% ethyl acetate in hexane); IR (thin film): $n_{max}$ 3359, 1729, 1631, 1516, 1308, 1258, 1158, 1093 cm$^{-1}$; $^1$H NMR (500 MHz, methanol-d$^4$): d 8.54 (d, *J* = 2.0 Hz, 1 H, Ar), 7.83-7.81 (m, 2 H, Ar), 7.74 (dd, *J* = 2.0, 9.0 Hz, 1 H, Ar), 7.52-7.43 (m, 3 H, Ar), 6.97 (d, *J* = 9.0 Hz, 1 H, Ar), 4.12 (dd, *J* = 6.0, 8.0 Hz, 1 H, CH), 3.64 (dd, *J* = 6.0, 13.5 Hz, 1 H, C*H*H), 3.47 (dd, *J* = 8.0, 13.5 Hz, 1 H, CH*H*), 1.25 (s, 9 H, $^t$Bu); $^{13}$C NMR (125 MHz, methanol-d$^4$): d 170.5, 168.3, 149.4, 142.2, 134.8, 133.6, 131.7, 130.1, 128.1, 127.1, 122.2, 119.9, 83.4, 57.3, 43.2, 27.9; FAB-HRMS calcd (M+Cs$^+$) 597.0420, found 597.0439.

**Synthesis of compound 70 as illustrated in Figure 10.** To a solution of amine **69** (0.23 grams, 0.50 mmol) in methanol (15 mL) at room temperature was added 10% Pd/C (0.10 g) under argon. The flask was then equipped with a balloon containing $H_{2(g)}$. After 8 hours, the reaction mixture was filtered

through a pad of celite and the solvent removed *in vacuo* to give **70** as a brownish-reddish oil (0.19 grams, 90%). $R_f$ = 0.11 (silica, 80% ethyl acetate in hexane); IR (thin film): $n_{max}$ 3360, 2979, 1729, 1625, 1582, 1542, 1508, 1447, 1369, 1310, 1248, 1160, 1093, 758, 721, 688, 590 $cm^1$; $^1H$ NMR (500 MHz, methanol-$d^4$): d 7.82-7.80 (m, 2 H, Ar), 7.53-7.49 (m, 1 H, Ar), 7.46-7.43 (m, 2 H, Ar), 7.11 (d, *J* = 2.0 Hz, 1 H, Ar), 7.05 (d, *J* = 2.0 Hz, 1 H, Ar), 6.64 (d, *J* = 8.5 Hz, 1 H, Ar), 4.08 (dd, *J* =7.5, 14.5 Hz, 1 H, CH), 3.61 (dd, *J* = 6.0, 13.5 Hz, 1 H, C*H*H), 3.47 (dd, *J* = 8.0, 13.5 Hz, 1 H, CH*H*), 1.22 (s, 9 H, $^t$Bu); $^{13}C$ NMR (125 MHz, methanol-$d^4$): d 170.8, 170.6, 142.1, 141.2, 134.8, 133.7, 130.1, 128.1, 124.5, 120.6, 116.5, 115.5, 83.3, 57.5, 43.1, 28.0; FAB-HRMS calcd ($M+Na^+$) 435.1702, found 434.1727.

**Synthesis of compound 71 as illustrated in Figure 10**. To a solution of the diamine **70** (0.092 grams, 0.20 mmol) in ethanol (20 mL) was added triethylamine (0.032 mL, 0.22 mmol) and phenyl isothiocyanate (0.028 mL, 0.22 mmol). After 14 hours, the solvent was removed *in vacuo* to give a brown residue which was purified by preparative thin layer chromatography (silica, 5% methanol in dichloromethane) to give **71** as a brown solid (0.082 grams, 69%). $R_f$ = 0.16 (silica, 5% methanol in dichloromethane); IR (thin film): $n_{max}$ 3316, 3061, 2978, 1729, 1624, 1504, 1448, 1368, 1309, 1252, 1159, 1092, 837, 733 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): d 8.15 (bs, 1 H, NH), 7.81 (d, *J* = 7.5 Hz, 2 H, Ar), 7.56-7.03 (m, 14 H), 6.78 (bs, 1 H, NHC=O), 6.58 (d, *J* = 8.0 Hz, 1 H, *H*$NSO_2$Ph), 4.51 (bs, 1 H), 4.05 (bs, 1 H), 3.67 (bs, 1 H), 1.20 (s, 9 H, $^t$Bu); $^1H$ NMR (500 MHz, $CDCl_3$): d 180.3, 168.6, 167.4, 147.0, 143.3, 139.6, 137.6, 132.7, 129.0, 128.4, 127.1, 126.6, 125.4, 123.5, 116.1, 83.2, 60.3, 56.5, 42.0, 27.5; FAB-HRMS calcd ($M+Cs^+$) 702.0821, found 702.0797.

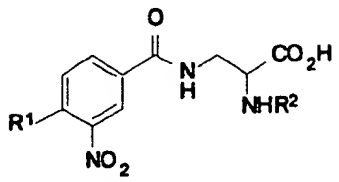
**Synthesis of compound 72 as illustrated in Figure 10**. To a solution of the thiourea **71** (0.077 grams, 0.14 mmol) in DMF (10 mL) at room temperature was added triethylamine (0.02 mL,

0.14 mmol) and mercury (II) chloride (0.04 grams, 0.14 mmol). After 4 hours, the reaction mixture was filtered through celite and rinsed with ethyl acetate. The solvent was removed *in vacuo* to give **72** as a brown residue (0.05 grams, 81%) which was carried onto the next step. $R_f$ = 0.32 (silica, 5% methanol in dichloromethane); $^1$H NMR (500 MHz, $CDCl_3$): d 7.98 (m, 2 H, Ar), 7.53-6.90 (m, 15 H, Ar), 4.16 (m, 1 H, CH), 3.83 (bs, 1 H, C*H*H), 3.62 (bs, 1 H, CH*H*), 1.25 (bs, 9 H, $^t$Bu); FAB-HRMS calcd ($M+Cs^+$) 668.0944, found 668.0923.

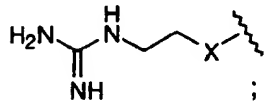
**Synthesis of compound 22 as illustrated in Figure 10**. Compound **22** was prepared by the same procedure as for **10** using **72** in lieu of **36b**. Yield: (0.04 grams, 88%). $R_t$ = 14.8 min; $^1$H NMR (500 MHz, methanol-$d^4$): d 7.85-7.82 (m, 3 H, Ar), 7.75 (dd, *J* = 1.5, 8.5 Hz, 1 H, Ar), 7.56-7.41 (m, 9 H, Ar), 4.22 (dd, *J* = 5.0, 9.0 Hz, 1 H, CH), 3.78 (dd, *J* = 5.0, 13.5 Hz, C*H*H), 3.48 (dd, *J* = 9.0, 13.5 Hz, CH*H*); $^{13}$C NMR (150 MHz, methanol-$d^4$): d 171.9, 169.2, 150.7, 141.6, 136.2, 133.1, 131.2, 130.9, 130.6, 129.5, 128.3, 127.5, 124.6, 124.1, 111.9, 111.8, 56.1, 42.8; FAB-HRMS calcd ($M+H^+$) 480.1342, found 480.1352.

What is claimed is:

1. An RGD mimetic represented by the following structure:



wherein $R^1$ is a radical selected from a group consisting of one of the following structures: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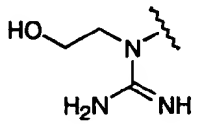
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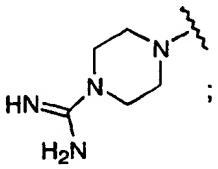
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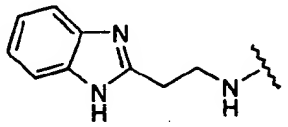
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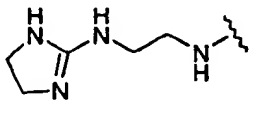
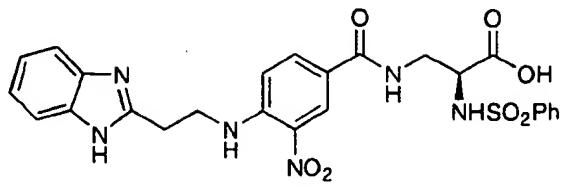

; and

X is a diradical selected from a group consisting of sulfur, -NH- and oxygen; $R^2$ is a radical selected from a group consisting of
$-CO_2$t-Butyl, -CO-Aryl and $-SO_2$-Aryl.

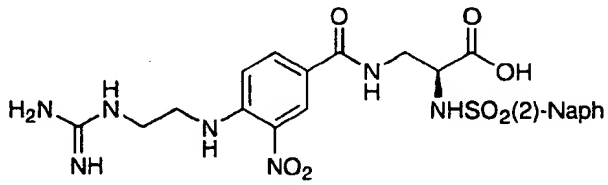
2. An RGD mimetic as described in claim 1 wherein **Aryl** is selected from a group consisting of phenyl, 1-naphthyl, and 2-naphthyl.

3. An RGD mimetic as described in claim 2 wherein $R^2$ is $-SO_2$-Aryl.

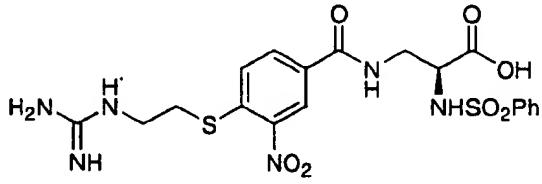
4. An RGD mimetic as described in claim 1 represented by the following structure:



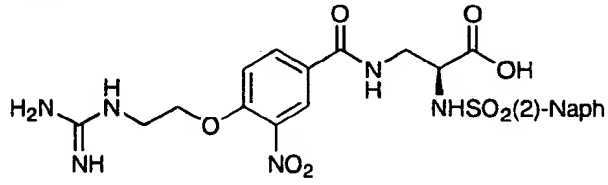
5. An RGD mimetic as described in claim 1 represented by the following structure:



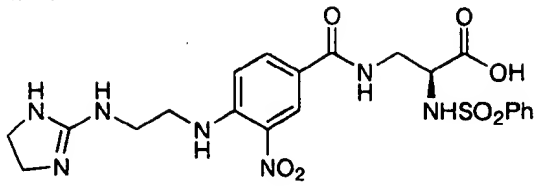
6. An RGD mimetic as described in claim 1 represented by the following structure:



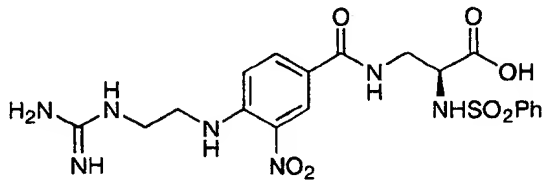
7. An RGD mimetic as described in claim 1 represented by the following structure:



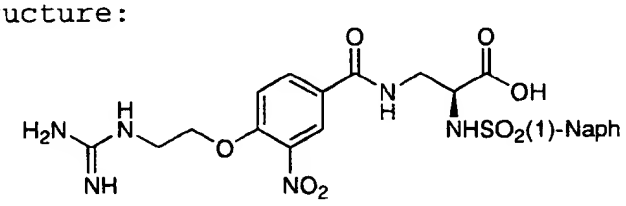
8. An RGD mimetic as described in claim 1 represented by the following structure:



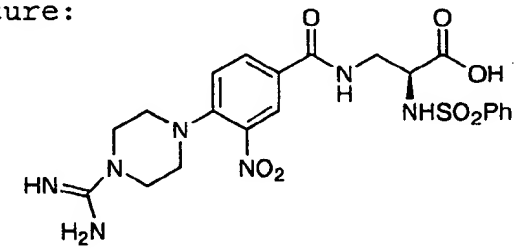
9. An RGD mimetic as described in claim 1 represented by the following structure:



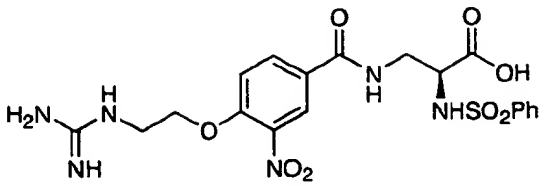
10. An RGD mimetic as described in claim 1 represented by the following structure:



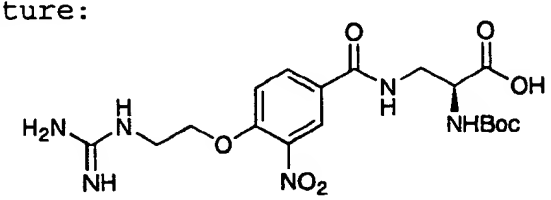
11. An RGD mimetic as described in claim 1 represented by the following structure:



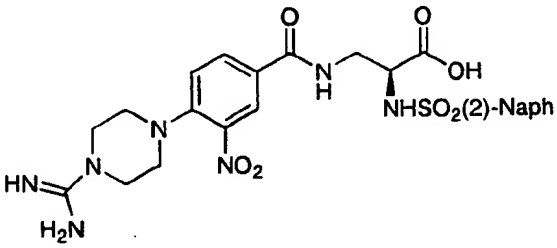
12. An RGD mimetic as described in claim 1 represented by the following structure:



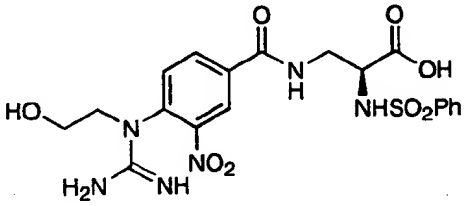
13. An RGD mimetic as described in claim 1 represented by the following structure:



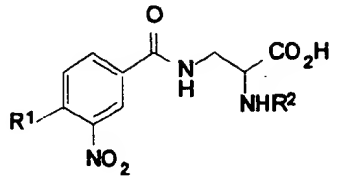
14. An RGD mimetic as described in claim 1 represented by the following structure:



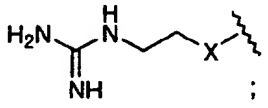
15. An RGD mimetic as described in claim 1 represented by the following structure:



16. A method for producing an RGD mimetic represented by the following structure:



wherein $R^1$ is a radical selected from a group consisting of one of the following structures: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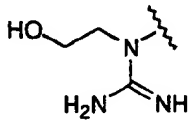
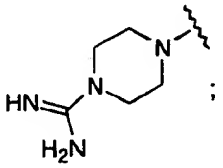
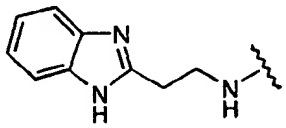
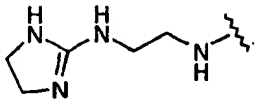
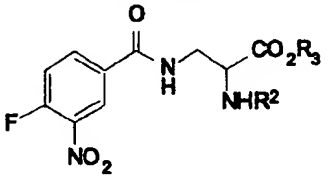

;

;


;

; and

X is a diradical selected from a group consisting of sulfur, -NH- and oxygen; $R^2$ is a radical selected from a group consisting of
$-CO_2t$-Butyl, -CO-Aryl and $-SO_2$-Aryl;

the method comprising the following steps:

Step 1: Providing a nitroaryl precursor having a fluoride group covalently attached to the nitroaryl ring represented by the following structure:

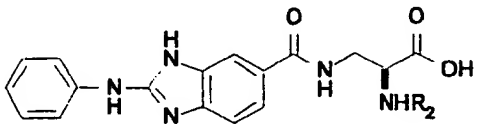


wherein $R_3$ is an acid protecting group; then

Step 2: Displacing the fluoride group with a nucleophile having a protected guanidine group using nucleophilic aromatic substitution for producing a protected RGD mimetic; and then

Step 3: Deprotecting the protected RGD mimetic with an acid for producing the RDG mimetic.

17. An RGD mimetic represented by the following structure:



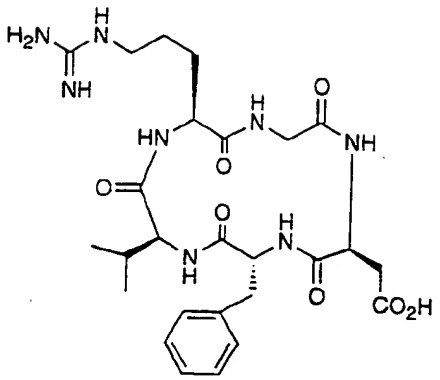
wherein $R^2$ is a radical selected from a group consisting of $-CO_2t$-Butyl, and $-SO_2$-Aryl.

18. An RGD mimetic as described in claim 17 wherein **Aryl** is selected from a group consisting of phenyl, 1-naphthyl, and 2-naphthyl.

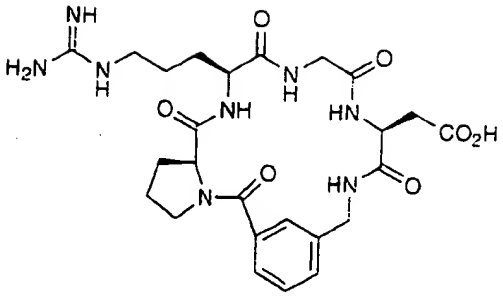
19. A process for differentially inhibiting $\alpha_{iib}\beta_3$ mediated cell adhesion over $\alpha_v\beta_3$ mediated cell adhesion comprising the following step:

contacting $\alpha_{iib}\beta_3$ expressing cells with a solution containing an RGD mimetic selected from the compounds of claims 5, 7, 9, 11, 14, or 15, said solution having a concentration of the RGD mimetic sufficient for inhibiting $\alpha_{iib}\beta_3$ mediated cell adhesion,

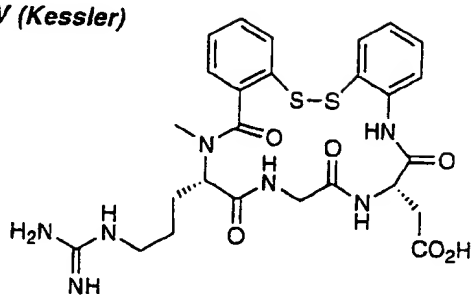
wherein $\alpha_{iib}\beta_3$ mediated cell adhesion is inhibited at least approximately 100 fold more than $\alpha_v\beta_3$ mediated cell adhesion.



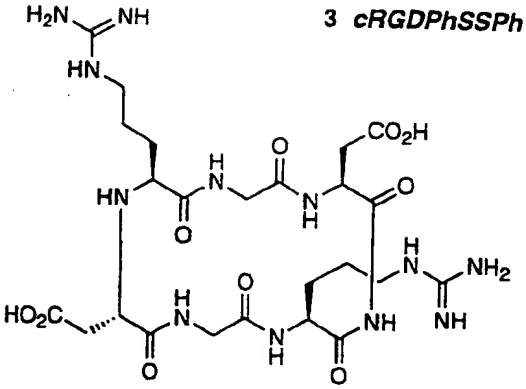
1 *cRGDFV (Kessler)*



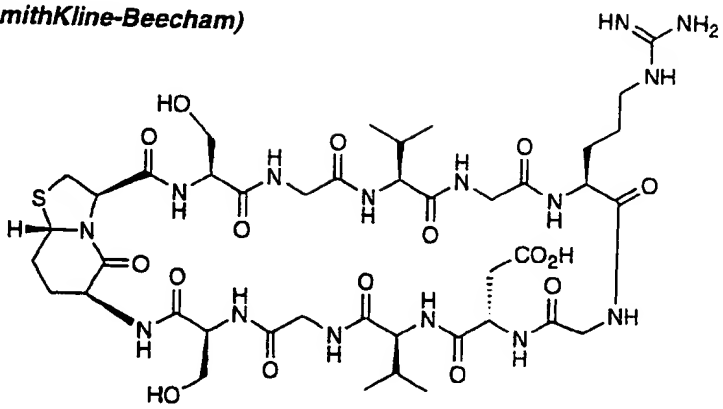
2 *cPRGD-Mamb (Dupont-Merck)*



3 *cRGDPhSSPh (SmithKline-Beecham)*

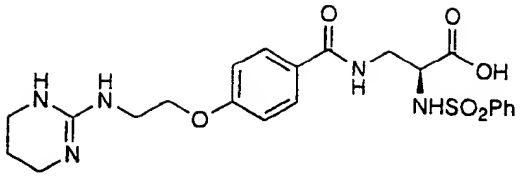


4 *cRGDRGD (Burgess)*

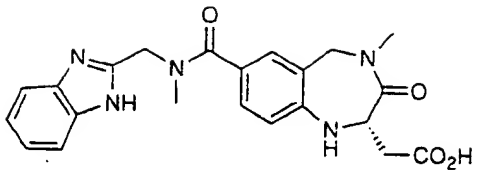


5 *cRGDVGS-BTD-SGVA (Goodman)*

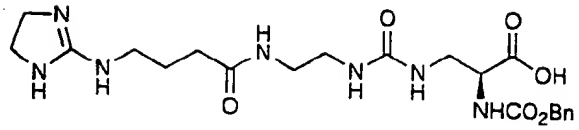
FIGURE 1



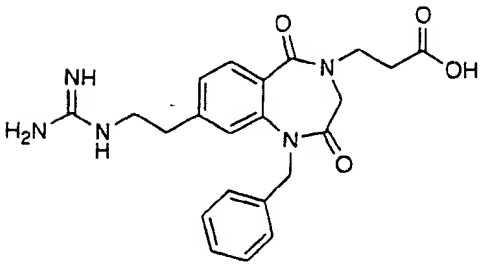
6 *(Merck)*



7 *(SmithKline-Beecham)*

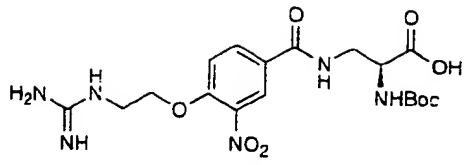


8 *(Dupont-Merck)*



9 *(Genentech)*

FIGURE 2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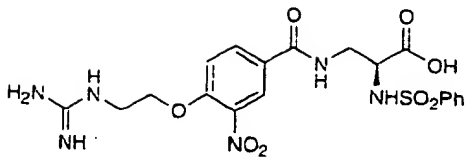
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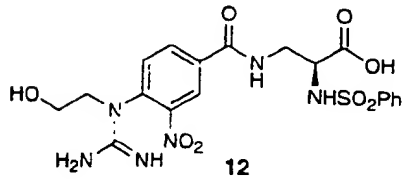
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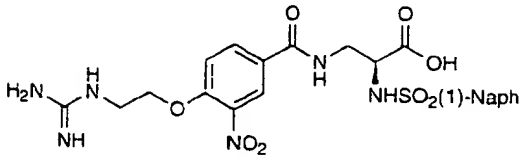
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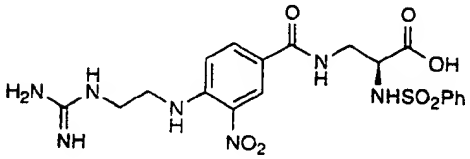
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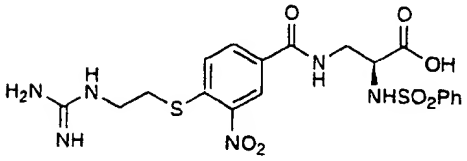
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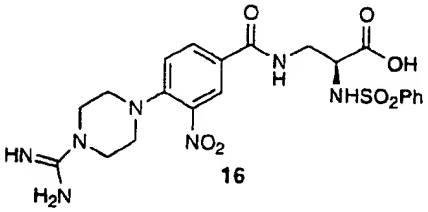
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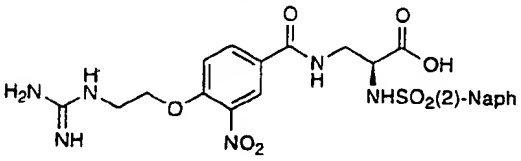
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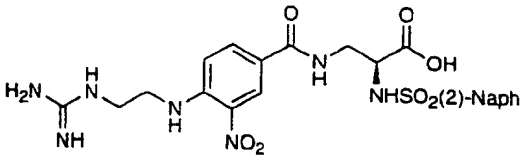
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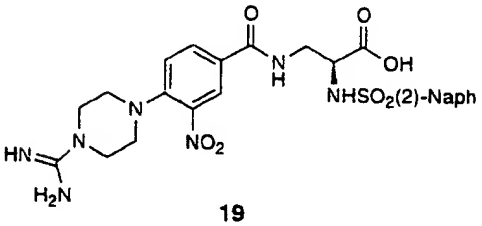
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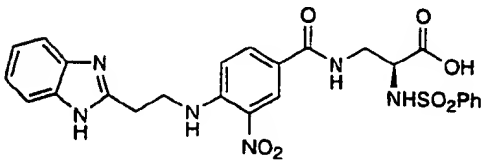
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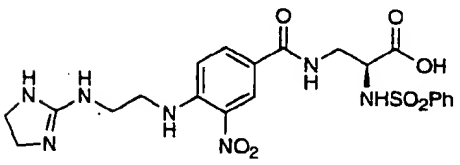
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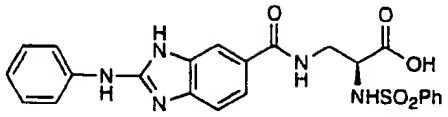
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FIGURE 3

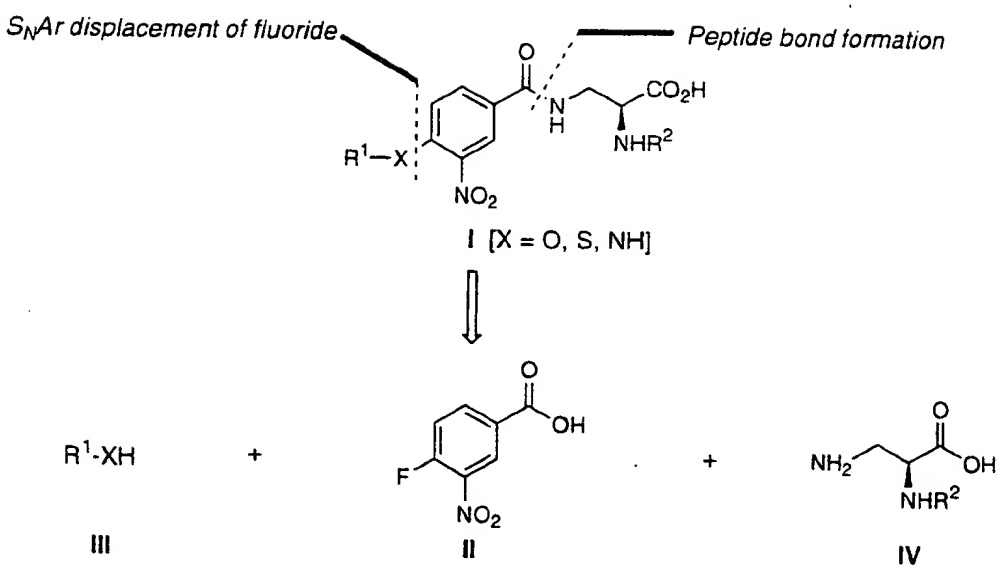
SNAr displacement of fluoride
Peptide bond formation
R1—X
NO2
CO2H
NHR2
I [X = O, S, NH]
R1-XH
III
F
OH
II
NH2
IV

FIGURE 4

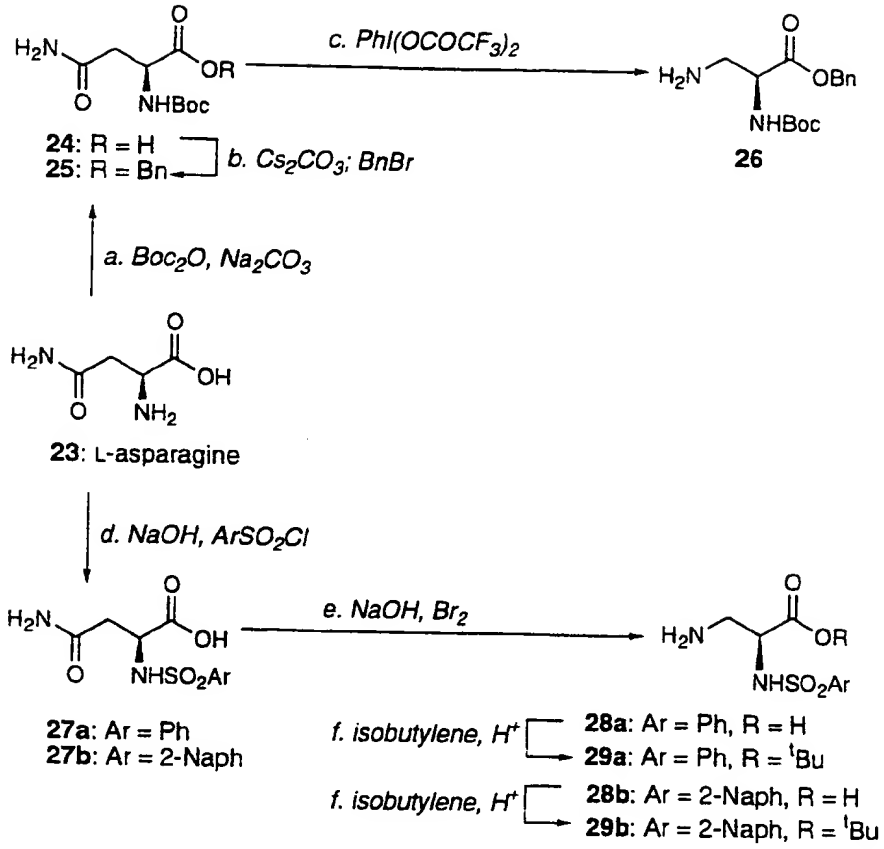
c. PhI(OCOCF3)2
24: R = H
25: R = Bn
b. Cs2CO3; BnBr
26
a. Boc2O, Na2CO3
23: L-asparagine
d. NaOH, ArSO2Cl
e. NaOH, Br2
27a: Ar = Ph
27b: Ar = 2-Naph
f. isobutylene, H+
28a: Ar = Ph, R = H
29a: Ar = Ph, R = tBu
f. isobutylene, H+
28b: Ar = 2-Naph, R = H
29b: Ar = 2-Naph, R = tBu

FIGURE 5

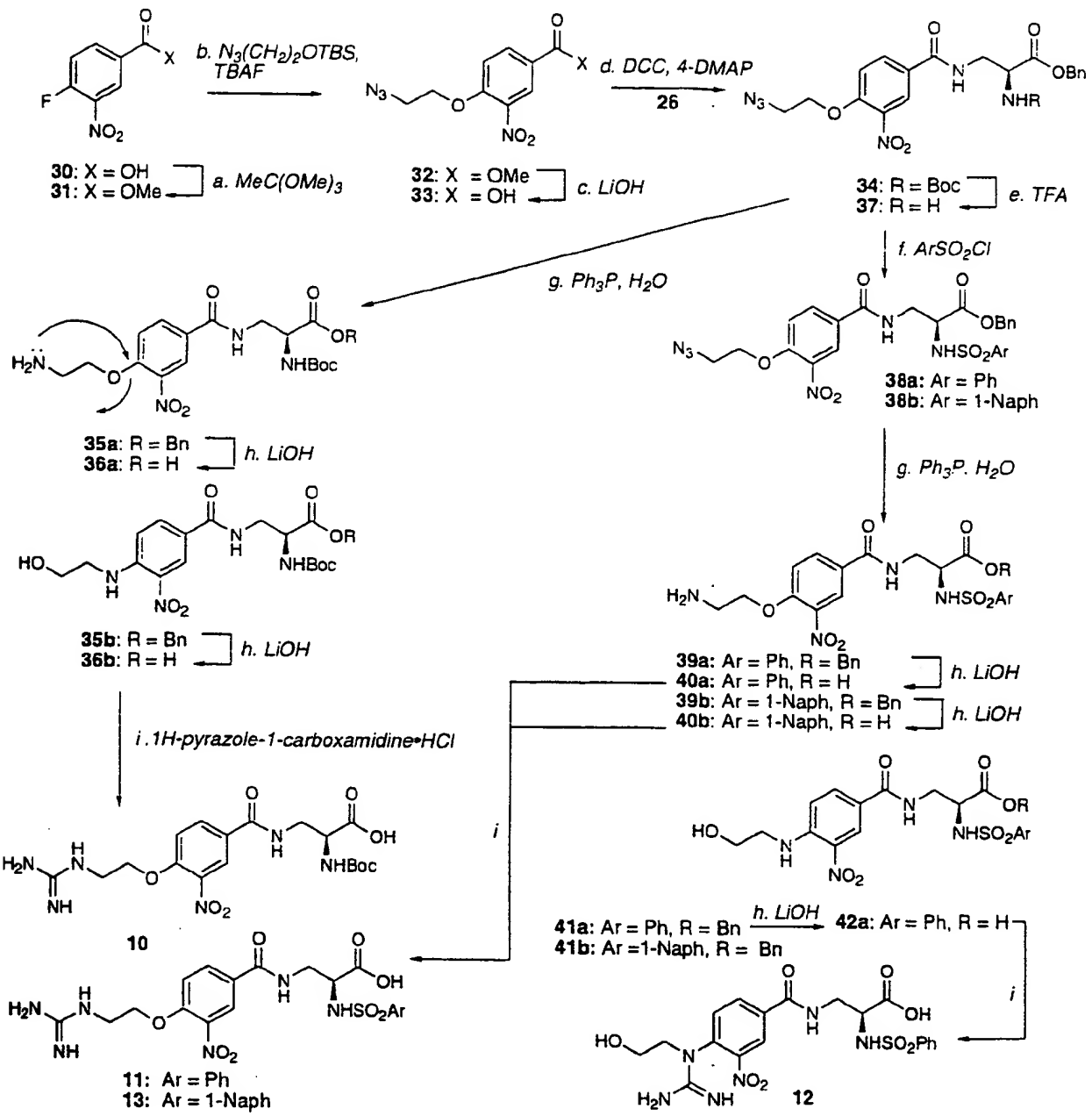
b. $N_3(CH_2)_2OTBS$, TBAF
d. DCC, 4-DMAP
26
30: X = OH
31: X = OMe
a. $MeC(OMe)_3$
32: X = OMe
33: X = OH
c. LiOH
34: R = Boc
37: R = H
e. TFA
f. $ArSO_2Cl$
g. $Ph_3P$, $H_2O$
35a: R = Bn
36a: R = H
h. LiOH
35b: R = Bn
36b: R = H
h. LiOH
38a: Ar = Ph
38b: Ar = 1-Naph
g. $Ph_3P$, $H_2O$
39a: Ar = Ph, R = Bn
40a: Ar = Ph, R = H
h. LiOH
39b: Ar = 1-Naph, R = Bn
40b: Ar = 1-Naph, R = H
h. LiOH
i .1H-pyrazole-1-carboxamidine•HCl
i
10
41a: Ar = Ph, R = Bn
41b: Ar =1-Naph, R = Bn
h. LiOH
42a: Ar = Ph, R = H
i
11: Ar = Ph
13: Ar = 1-Naph
12

FIGURE 6

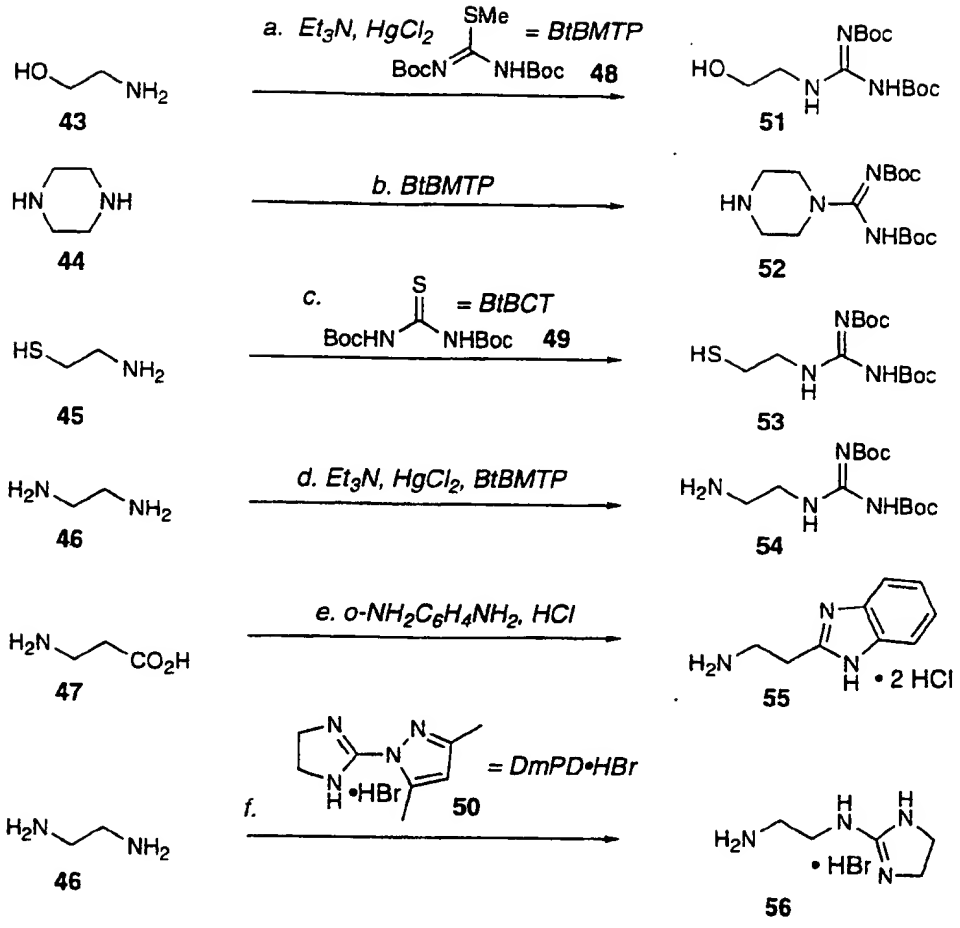
a. Et3N, HgCl2
SMe
= BtBMTP
BocN
NHBoc 48
HO
NH2
43
NBoc
HO
N
H
NHBoc
51
b. BtBMTP
HN
NH
44
HN
N
NBoc
NHBoc
52
c.
S
= BtBCT
BocHN
NHBoc 49
HS
NH2
45
HS
NBoc
N
H
NHBoc
53
d. Et3N, HgCl2, BtBMTP
H2N
NH2
46
H2N
NBoc
N
H
NHBoc
54
e. o-NH2C6H4NH2, HCl
H2N
CO2H
47
N
N
H2N
N
H
• 2 HCl
55
f.
N
N
N
N
H
•HBr
50
= DmPD•HBr
H2N
NH2
46
H
N
H
N
H2N
• HBr
N
56

FIGURE 7

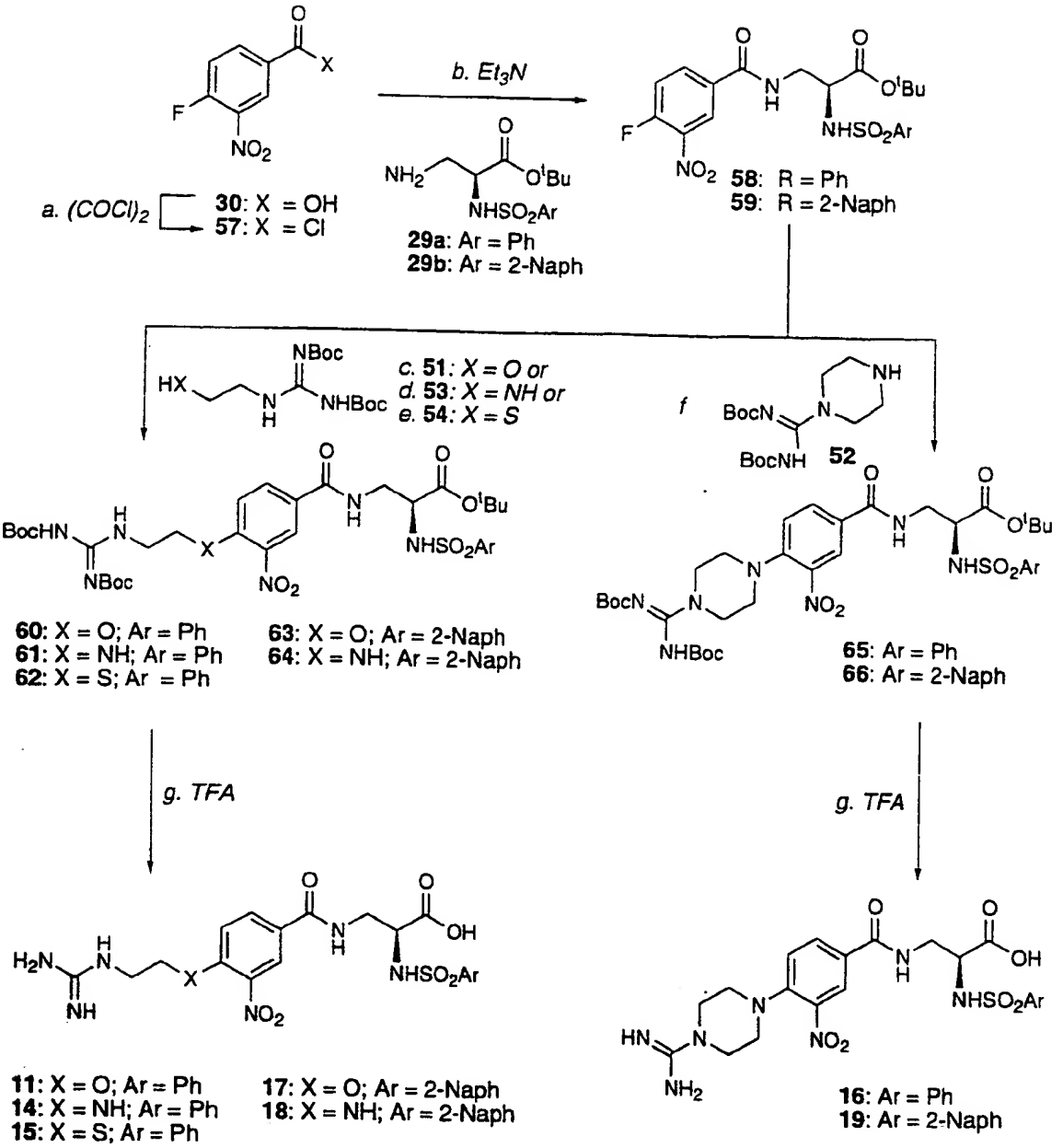
a. (COCl)2
30: X = OH
57: X = Cl
b. Et3N
29a: Ar = Ph
29b: Ar = 2-Naph
58: R = Ph
59: R = 2-Naph
c. 51: X = O or
d. 53: X = NH or
e. 54: X = S
f
52
60: X = O; Ar = Ph
61: X = NH; Ar = Ph
62: X = S; Ar = Ph
63: X = O; Ar = 2-Naph
64: X = NH; Ar = 2-Naph
65: Ar = Ph
66: Ar = 2-Naph
g. TFA
g. TFA
11: X = O; Ar = Ph
14: X = NH; Ar = Ph
15: X = S; Ar = Ph
17: X = O; Ar = 2-Naph
18: X = NH; Ar = 2-Naph
16: Ar = Ph
19: Ar = 2-Naph

FIGURE 8

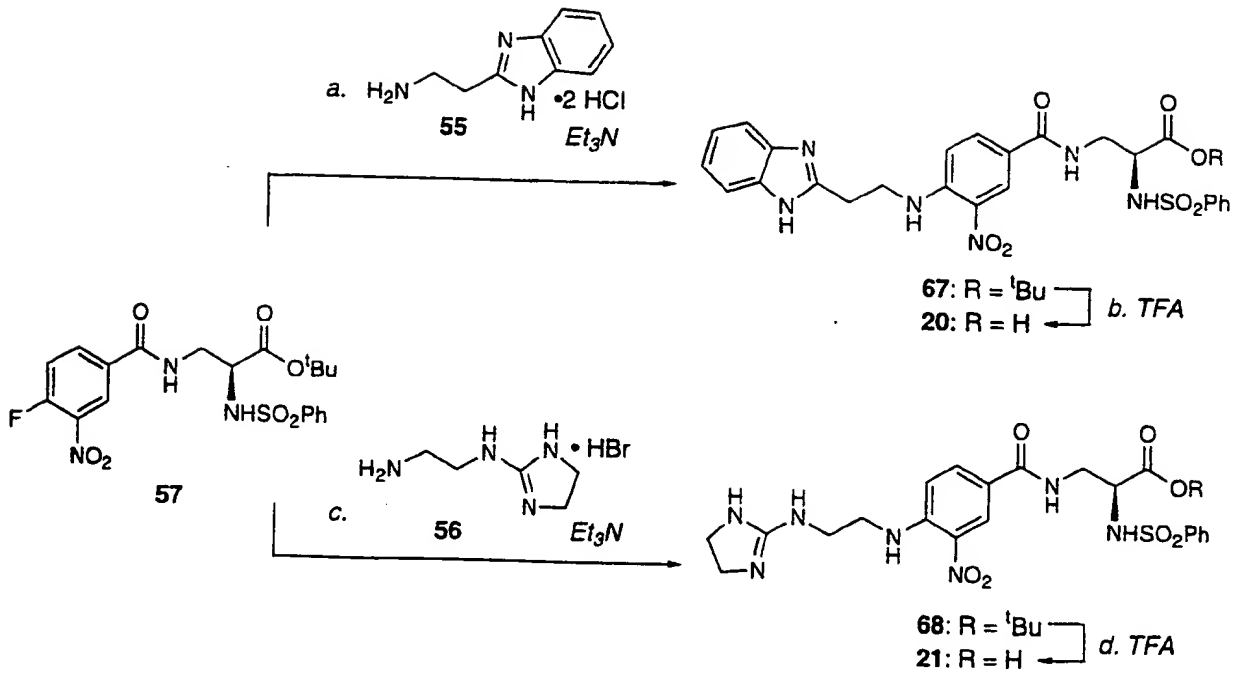
a. H2N
•2 HCl
55
Et3N
67: R = tBu
20: R = H
b. TFA
57
c.
56
Et3N
68: R = tBu
21: R = H
d. TFA

FIGURE 9

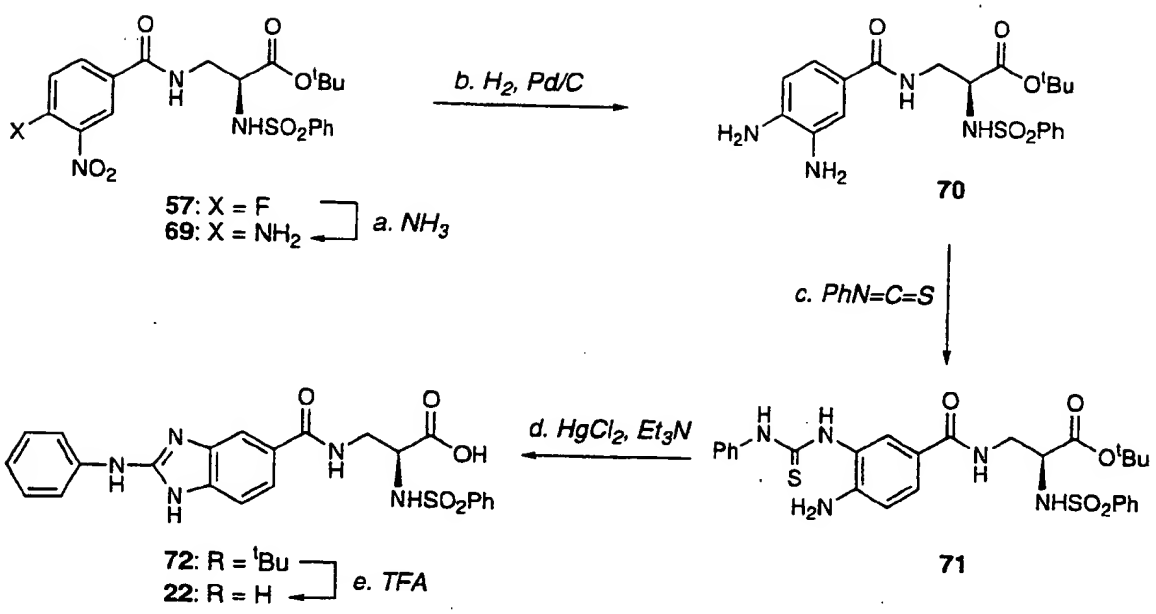
b. $H_2$, Pd/C
57: X = F
69: X = $NH_2$
a. $NH_3$
70
c. PhN=C=S
d. $HgCl_2$, $Et_3N$
71
72: R = tBu
22: R = H
e. TFA

FIGURE 10

| Integrin | $\alpha_v\beta_3$ | | $\alpha_v\beta_5$ | | $\alpha_{II\,b}\beta_3$ | |
|---|---|---|---|---|---|---|
| Compound # | $IC_{50}$ | cQ | $IC_{50}$ | cQ | $IC_{50}$ | cQ |
| | M | | M | | M | |
| GRGDSPK | 3.2E-07 | 1.0E+02 | > | 9.9E+01 | 6.0E-06 | 9.3E-01 |
| 1 | 3.1E-09 | 1.0E+00 | 1.8E-06 | 1.0E+00 | 6.4E-06 | 1.0E+00 |
| 20 | 8.10E-10 | 2.60E-01 | > | | 240E-08 | 3.70E-03 |
| 18 | 1.60E-09 | 4.00E-01 | 1.60E-06 | 7.00E-01 | 1.70E-11 | 2.70E-06 |
| 15 | 3.00E-09 | 9.80E-01 | 3.50E-06 | 1.90E+00 | 1.30E-10 | 2.00E-05 |
| 17 | 3.80E-09 | 1.20E+00 | 2.10E-06 | 1.20E+00 | 3.60E-10 | 5.60E-05 |
| 21 | 9.50E-09 | 3.10E+00 | 5.00E-06 | 2.80E+00 | 9.00e-10 | 1.40E-04 |
| 14 | 3.90E-08 | 1.20E+01 | 8.30E-06 | 4.60E+00 | 6.70E-10 | 1.10E-04 |
| 13 | 4.40E-08 | 1.40E+01 | > | | 1.40E-08 | 2.10E-03 |
| 16 | 9.60E-08 | 3.00E+01 | > | | 8.70E-10 | 1.40E-04 |
| 11 | 1.00E-07 | 3.30E+01 | > | | 1.20E-08 | 1.90E-03 |
| 10 | 4.00E-07 | 1.30E+02 | 9.00E-06 | 5.00E+00 | 2.10E-06 | 3.30E-01 |
| 19 | 4.80E-07 | 1.50E+02 | > | | 3.60E-11 | 5.60E-06 |
| 22 | 1.50E-06 | 4.70E+02 | > | | 6.50E-08 | 1.00E-02 |
| 12 | 1.90E-06 | 6.00E+02 | > | | 4.90E-10 | 7.60E-05 |

FIGURE 11

| Cell Line | M21 | UCLA-P3 | M21-L |
|---|---|---|---|
| Ligand | VN | VN | Fg |
| Integrin⇒ | $\alpha_v\beta_3$ / ($\alpha_v\beta_5$) | $\alpha_v\beta_5$ | $\alpha_{IIb}\beta_3$ |
| Compound # | $IC_{50}$ M | $IC_{50}$ M | $IC_{50}$ M |
| GRGDSPK | 3.3E-05 | 4.0E-05 | 7.5E-05 |
| 1 | 6.6E-06 | 1.7E-06 | >1.0E-04 |
| | | | |
| 15 | 1.3E-06 | 8.3E-07 | 1.5E-07 |
| 21 | 2.0E-06 | 6.0E-06 | 5.0E-07 |
| 18 | 3.3E-06 | 3.6E-06 | 2.0E-08 |
| 17 | 8.7E-06 | 1.8E-06 | 4.4E-08 |
| 14 | 1.1E-05 | 9.0E-06 | 1.3E-07 |
| 20 | 1.4E-05 | 4.0E-05 | 1.0E-05 |
| 13 | 4.0E-05 | 1.5E-05 | 2.5E-06 |
| 16 | 4.5E-05 | 3.3E-05 | 1.4E-08 |
| 10 | 6.0E-05 | 1.5E-05 | 4.5E-05 |
| 11 | 7.5E-05 | 4.5E-05 | 2.5E-06 |
| 19 | 9.5E-05 | 4.7E-05 | 1.4E-08 |
| 22 | >1.0E-04 | >1.0E-04 | 3.5E-05 |
| 12 | >1.0E-04 | 5.0E-05 | 2.0E-07 |

FIGURE 12

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/15252

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :A61K 31/435; C07D 487/04
US CL :514/300; 544/336, 358

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/300; 544/336, 358

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 5,741,796 A (HARTMAN et al) 21 April, col. 2-6, | 1,2,3 in part,5-7,9, 10,12,13,15,16 in part and 19 |
| Y | STEWART et al., Reaction Mechanisms Displayed by Catalytic Antibodies, Accounts Chem Res., 1993. Vol 26. pages 396-398. | 1,2 and3 in part 5- 7,9, 10,12,13,15 ,16 in -part and 19 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | | | |
|---|---|---|---|
| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" | earlier document published on or after the international filing date | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family |
| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

| | |
|---|---|
| Date of the actual completion of the international search<br>03 NOVEMBER 1999 | Date of mailing of the international search report<br>17 NOV 1999 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>PK SREPADA<br>Telephone No. (703) 308-4717 |

Form PCT/ISA/210 (second sheet)(July 1992)*

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/15252

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ **Claims Nos.:**
**because they relate to subject matter not required to be searched by this Authority, namely:**

2. ☐ **Claims Nos.:**
**because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:**

3. ☐ **Claims Nos.:**
**because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).**

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1,2,and 3(in part),5-7,9,10,12,13,15, 16(in part),19 drawn to R1 being non-cyclic amino,corresponding method of preparation and use

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/15252

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1,2 and 3(in part),5-7,9,10,12,13,15, 16(in part),19 drawn to R1 being non-cyclic amino, corresponding method of preparation and use.
Group II, claim(s)1(in part),11,14 and 16 drawn to R1 being piperazine.
Group III, claim(s)1 (in part),4,8,16-18 , drawn to R1 being monocyclic imidazole and bicyclic ring wherein imidazole is fused to benzene ring.

The inventions listed as Groups I-III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The groups as outlined above are not so linked as to form a single inventive concept as they are drawn to structurally dissimilar compounds of varying cores and functional moieties.